SOME NEW STRATEGIES OF DIRECTION, PROTECTION, AND ACTIVATION IN LITHIATION CHEMISTRY

BY

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To My Parents and My Wife, Ming, with Love

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS iii

ABSTRACT vii

CHAPTERS

I BENZOTRIAZOLE-ASSISTED SYNTHESES OF SYMMETRICAL SECONDARY AND TERTIARY AMINES, AND OF N,N-DI-SUBSTITUTED HYDROXYLAMINES 1

1.1 Introduction 1

1.1.1 Aim of the Work.....6

1.2. Results and Discussion 10

1.2.1 Preparation of Benzotriazole Derivatives 10

1.2.2 Preparation of Secondary and Tertiary Amines, and of N,N-Di-substituted Hydroxylamines 12

1.3 Conclusions.....15

1.4 Experimental.....16

II α-LITHIATION OF PYRAZOLES 28

2.1 Introduction 28

2.1.1 Generation of α-Carbanions by the Protection Route 29

2.1.2 Generation of α-Carbanions by the Protection-Activation Route 32

2.1.3 Carbon Dioxide, Aminals and Hemi-aminals as "Protecting-Activating" Groups.....36

2.1.4 Aim of the Work.....43

2.2 Results and Discussion 46

2.3 Conclusions 55

2.4 Experimental 55

III α-LITHIATION OF 1,2,4-TRIAZOLES 63

3.1 Introduction 63

3.1.1 The Important Industrial Applications of 3(5)-Substituted 1,2,4-Triazoles 63

3.1.2 General View of the Methods for the Preparation of 3(5)-Substituted 1,2,4-Triazoles 65

3.1.3 General View of the Lithiation of 1,2,4-Triazoles 68

3.1.4 Aim of the Work 72

3.2 Results and Discussion 75

3.2.1 Preparation of 1-(1-Pyrrolidinomethyl)-1.2.4-triazole.....75

3.2.2 Lithiation of 1-(1-Pyrrolidinomethyl)-1.2.4-triazole 76

3.2.3 Deprotection of 3-Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazole 93

3.3 Conclusions 99

3.4 Experimental 100

IV DIRECTED LITHIATION OF BENZENESULFINAMIDES 114

4.1 Introduction 114

4.1.1 General Aspects of Directed Lithiation Reactions 115

4.1.2 Aim of the Work.....118

4.2 Results and Discussion 126

4.2.1 Preparation of N-Phenyl Arene-sulfinamides.....126

4.2.2 Directed Lithiation of N-Phenyl Arenesulfinamides.....128

4.2.3 Desulfination of Trisubstituted Sulfinamides 137

4.3 Conclusions 141

4.4 Experimental.....142

V. SUMMARY 156

BIBLIOGRAPHY 160

BIOGRAPHICAL SKETCH 178

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SOME NEW STRATEGIES OF DIRECTION, PROTECTION, AND ACTIVATION IN LITHIATION CHEMISTRY

By

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Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

Some new strategies for the direction, protection, and activation in lithiation chemistry have been investigated in this work. Particular attention has been focused on the elaboration of these strategies in the α-lithiation of azoles (pyrazole and 1,2,4-triazole) and in the directed lithiation of benzenesulfinamides. The utilization of benzotriazole as an auxiliary in the synthetic transformations to secondary and tertiary amines, and to N,N-disubstituted hydroxylamines has also been investigated.

The good leaving ability of benzotriazole enabled the nucleophilic displacement of the benzotriazole moieties with Grignard reagents and organolithium reagents in N,N-bis(benzotriazol-1-ylmethyl)amine, -N-alkylamines

and -hydroxylamine, leading to the formation of various secondary and tertiary amines and N,N-disubstituted hydroxylamines involving two new C-C bonds.

The use of formaldehyde as the equivalent of a protecting-activating group was found to be effective in the α-lithiation of pyrazole. The lithiation afforded the dilithio species efficiently at low temperature, and the anion was reactive towards a variety of electrophiles. The introduction and the removal of the protecting group were readily accomplished under mild conditions.

The use of aminals as protecting-activating groups to enable the α-lithiation of azoles was investigated. 1-(1-Pyrrolidinomethyl)-1,2,4-triazole was readily lithiated at the α-carbon atom. The α-substituted 1,2,4-triazoles exist in solution as mixtures of 3- and 5-substituted isomers, the 3-substituted isomer predominating in most cases. Deprotection of the aminal group was achieved by reductive elimination using sodium borohydride.

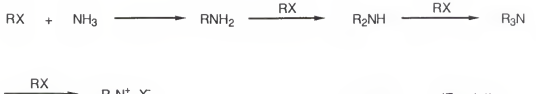
A synthetic strategy for the construction of meta-substituted benzene derivatives via the directed lithiation methodology was investigated. The directed lithiation of benzenesulfinamides was successfully achieved and a variety of substituents was introduced ortho to the sulfinamide group. Desulfination was accomplished by mercuridesulfination or reductive desulfination using Raney-Nickel.

CHAPTER I

BENZOTRIAZOLE-ASSISTED SYNTHESES OF SYMMETRICAL SECONDARY AND TERTIARY AMINES, AND OF N,N-DISUBSTITUTED HYDROXYLAMINES

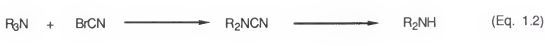
1.1 Introduction

Although numerous methods are available for the preparation of secondary and tertiary amines [79MI1], most of these methods have disadvantages or limitations. For example, the most straightforward route to secondary and tertiary amines is the alkylation of ammonia or a primary amine with an alkyl halide. However, the reaction generally leads to a mixture of primary, secondary and tertiary amines, and even quaternary salts, since the reaction cannot be expected to stop at any specific stage on the basis of intrinsic differences in amine nucleophilicity. The separation of pure products thus becomes tedious and this usually leads to low yields. Satisfactory preparation of secondary amines by such alkylation procedures usually requires temporary protection of one nitrogen position by a protecting group such as $ArSO_2$- [68MI1], F_3CSO_2- [73TL3839], $(EtO)_2PO$- [77AG(E)107], or -CN [82CA162070].

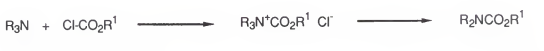


(Eq. 1.1)

Dealkylation of tertiary amines with cyanogen bromide (BrCN) or with acid chlorides readily gives secondary amines (Equation 1.2, 1.3, respectively) [67JCS(C)2015, 77TL1567], but the availability of a starting material more complex than the product is required.



(Eq. 1.2)

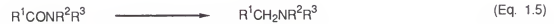


(Eq. 1.3)

Alkylation of secondary amines is a useful tool for the synthesis of tertiary amines. However, in unhindered cases there is a danger of over-reaction to yield quaternary salts, while sterically hindered tertiary amines are not easy to prepare in this way, as the reactions are slow and the yields low to moderate [60JA4908, 78S766].

Preparation of tertiary amines by the reduction of iminium salts (largely confined to formaldehyde derivatives) or tertiary amides [79MI1] (Equations 1.4, 1.5, respectively) requires availability of the appropriate precursor and does not allow for structural versatility in the product [79MI1].

(Eq. 1.4)



(Eq. 1.5)

Reductive dealkylation of quaternary ammonium salts [79MI1], often gives good yields of tertiary amines but the starting material is usually itself made from a tertiary amine. Deamination of dimethylhydrazinium salts [82SC801] affords N,N-dimethyl-alkyl- or -arylamines in high yields, but involves the carcinogenic N,N-dimethylhydrazine (Equation 1.6).

(Eq. 1.6)

Reaction of imines [79MI1] or iminium salts [75CB2827, 85LA2178, 81JOM275] with organometallic reagents provides a useful route to structurally diverse secondary and tertiary amines (Equation 1.7 and 1.8); however, the required intermediates are often unstable and very hygroscopic [63JOC302, 71AG(E)330].

In a similar fashion, tertiary amines have also been prepared by the reaction of organometallic derivatives with various compounds of type R_2NCH_2X such as alkoxymethylamines [23JCS532], α-dialkylaminonitriles [32JCS2607], chloromethylamines [73CB69], or phenylthiomethylamines [67JOC2892]; however, none of these starting materials are readily available.

Methods for the synthesis of N,N-disubstituted hydroxylamines have been reviewed [72OPP135]. Symmetrical N,N-dialkyl hydroxylamines $(RCH_2)_2NOH$ have been prepared by the direct alkylation of hydroxylamine with alkyl halides [1899JCS792, 19JA674, 63JOC1068] in the presence of a base (Equation 1.9). However, the reaction always yields a mixture of monoalkyl and dialkyl hydroxylamines irrespective of the ratio of the alkyl halides and hydroxylamine employed.

$$H_2NOH + RX \longrightarrow RNHOH \xrightarrow{RX} R_2NOH \qquad \text{(Eq. 1.9)}$$

The reaction of nitrosyl chloride or nitrogen dioxide with Grignard reagents provides routes to the preparation of dialkylhydroxylamines [59CB2606, 56CB396], but yields are very low. The reaction of Grignard reagents with alkyl nitrates and nitrites provides dialkylhydroxylamines in comparatively better yields [21JCS251] (Equations 1.10, 1.11, respectively), however the starting materials are less accessible and less stable.

$$R^1ONO_2 + 2\ R^2MgX \longrightarrow R^2{}_2NOH \qquad \text{(Eq. 1.10)}$$

$$R^1ONO + 2\ R^2MgX \longrightarrow R^2{}_2NOH \qquad \text{(Eq. 1.11)}$$

Oxidation of secondary amines with hydrogen peroxide or an acyl peroxide gives N,N-disubstituted hydroxylamines, but the method is erratic and reported yields never exceeded 50%. Further, oxidation of the α-carbon atoms often occurs to produce complex mixtures of products.

The thermal decomposition (Cope reaction) of tertiary amine N-oxides [55MI1] appears to be a useful tool for the

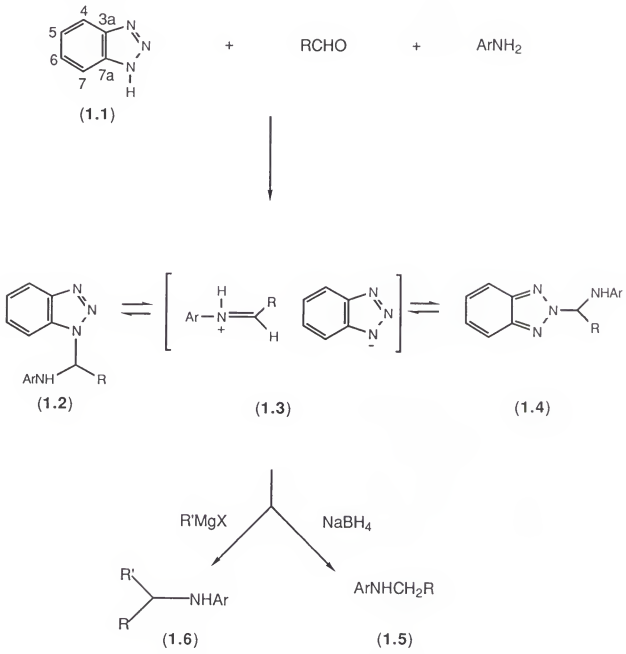
synthesis of N,N-disubstituted hydroxylamines. Unfortunately, if the amine oxide possesses more than one type of alkyl group capable of forming an olefin, a mixture of hydroxylamines is often obtained.

In view of the continuous interest in the physiological properties of amines [59BP814152, 61MI1, 62BEP617762, 63ZAP728, 79MI1, 87AG(E)320], new general methods for their preparation are of considerable significance.

1.1.1 Aim of the Work

The objective of the present project was to develop methods of considerable generality for the preparation of secondary and tertiary amines, and of N,N-disubstituted hydroxylamines. Previous work by Katritzky et al. [87JCS(P1)799, 87JCS(P1)805] has already amply demonstrated the utility of the benzotriazole group as an auxiliary in synthesis, in particular in the elaboration of the nitrogen functionality. Results previously obtained have shown that the readily available derivatives (1.2) (and in its isomeric form 1.4) synthesized by the amino-alkylation of benzotriazole (1.1) were reduced easily with sodium borohydride to afford high yields of N-alkyl aryl-amines (1.5) [87JCS(P1)799] (Scheme 1.1). In a similar manner, the nucleophilic displacement of the benzotriazole moiety in derivatives (1.2) with Grignard reagents

afforded α-alkylated secondary amines (**1.6**) in high yields [87JCS(P1)805] (Scheme 1.1).

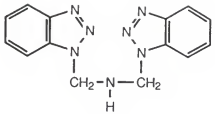


Scheme 1.1

Further elaboration of this strategy towards the synthesis of N-alkylated amides [88JCS(P1)2339] and thioamides [88TL1755, 88JOC5854] was also achieved successfully.

These results, together with mechanistic studies of benzotriazole derivatives [75JCS(P1)1181, 87JCS(P1)2673], revealed that benzotriazole aminal derivatives exist in solution as equilibrium mixtures of benzotriazol-1-yl and benzotriazol-2-yl isomers (such as **1.2** and **1.4**) which interchange *via* their ionic intermediates (such as **1.3**). Consequently, the carbon atom attached to the benzotriazole and the amine nitrogens must possess enhanced electrophilicity and therefore is expected to undergo reactions readily with various nucleophiles.

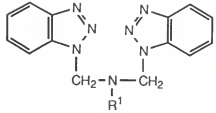
Results obtained previously encouraged us to carry out further investigations on the synthetic utility of benzotriazole derivatives of type (**1.7**), (**1.9**) and (**1.11**) which were expected to undergo facile alkylation upon reaction with Grignard reagents, thereby converting them into the corresponding variably substituted secondary amines (**1.8**), tertiary amines (**1.10**) and N,N-disubstituted hydroxylamines (**1.12**) (Scheme 1.2). Since Grignard reagents are readily available, these methods could be expected to show considerable generality for the preparation of the title compounds.



(1.7)

$\xrightarrow{R^2MgX}$ $(R^2CH_2)_2NH$

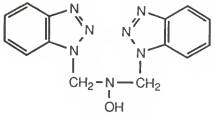
(1.8)



(1.9)

$\xrightarrow{R^2MgX}$ $(R^2CH_2)_2NR^1$

(1.10)



(1.11)

$\xrightarrow{R^2MgX}$ $(R^2CH_2)_2NOH$

(1.12)

Scheme 1.2

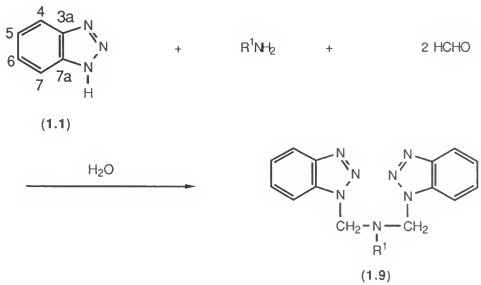
1.2 Results and Discussion

1.2.1 Preparation of Benzotriazole Derivatives (1.7), (1.9) and (1.11)

The preparation of benzotriazole derivatives (1.7), (1.9) and (1.11) has been reported previously [87JCS(P1)799]. Derivative (1.7) was obtained by the reaction of 1-hydroxymethylbenzotriazole with aqueous ammonia in methanol at room temperature, in the presence of acetic acid. It is essential that the aqueous ammonia solution should be neutralized with acetic acid, otherwise the reaction is sluggish and results in a low yield of product. In an alternative way, (1.7) was prepared by mixing ammonium acetate and 1-hydroxymethylbenzotriazole in acetonitrile and methanol.

Considerable improvement was achieved in the preparation of derivatives (1.9) and (1.11). Previously, derivatives (1.9) were prepared by refluxing 1-hydroxymethylbenzotriazole with a primary aliphatic amine and acetic acid in ethanol. This method provided derivatives (1.9) in good yields; however, the final products were actually obtained *via* a two-step procedure since 1-hydroxymethylbenzotriazole itself was prepared separately. Furthermore, simultaneous formation of monoalkylated derivatives and consequent isolation

difficulties were also encountered [87JCS(P1)799]. It was then found that derivatives (**1.9**) can be readily prepared by treatment of benzotriazole with a primary amine and formaldehyde in water solution at room temperature (Scheme 1.3). The reaction proceeded smoothly and afforded derivatives (**1.9**) e.g. (**1.9b**, R = C_8H_{17}) exclusively and in high yields. This method is obviously superior to the previous one since the reaction can be accomplished in one step. In addition, the manipulation is simple and no side products are formed. This methodology has been applied to the preparation of a series of N,N-bis(benzotriazol-1-yl-methyl)-N-alkylamines [90JCS(P1)541].



(**1.1**)

(**1.9**)

1.9b, R = C_8H_{17}

Scheme 1.3

The synthetic procedure previously reported for the preparation of N,N-bis(benzotriazol-1-ylmethyl)hydroxylamine (1.11) was treatment of 1-hydroxymethylbenzotriazole with hydroxylamine hydrochloride in an aqueous solution, neutralized with sodium hydrogen carbonate. However, by direct addition of hydroxylamine hydrochloride (without neutralization) to a solution of 1-hydroxymethylbenzotriazole, the yield increased dramatically from 44% to 87%. Apparently, the reaction is favored in acidic media.

1.2.2 Preparation of Secondary and Tertiary Amines, and of N,N-Disubstituted Hydroxylamines

When bis(benzotriazol-1-ylmethyl)amine (1.7) was treated with a Grignard reagent at room temperature followed by gentle reflux, the two benzotriazole moieties were readily displaced by alkyl groups, leading to the symmetrical secondary amine (1.8a-c). Generally, the Grignard reagents were prepared conventionally in diethyl ether, but the bis(benzotriazol-1-ylmethyl)amine (1.7) was added in a tetrahydrofuran solution because of its low solubility in diethyl ether. In addition, the amount of the Grignard reagent was usually in a four-fold excess since compound (1.7) bears an active proton which can react with and decompose one mole of the Grignard reagent.

The reactions were generally complete within one hour. The free benzotriazole, which was formed along with the amines after hydrolysis of the reaction mixture, was easily removed by extraction with alkali (2N NaOH). By-products from the coupling reaction of the Grignard reagent were routinely observed and were removed either by column chromatography or by acid extraction of the amine followed by neutralization of the obtained salt.

In a similar fashion, N,N-bis(benzotriazol-1-yl-methyl)-N-alkylamines (**1.9a**) and (**1.9b**) reacted with Grignard reagents in THF-Et_2O to give the corresponding tertiary amines (**1.11a-d**) in high yields. Since there are no active protons in derivatives (**1.9**), only a two-fold excess of the Grignard reagent was used. Although the substitutions of the benzotriazole moieties with the alkyl groups presumably occurred stepwise, no products of partial reaction were detected in these transformations.

The reactions of N,N-bis(benzotriazol-1-ylmethyl)-hydroxylamine (**1.11**) with various Grignard reagents were carried out in a similar way to those described for compound (**1.7**). Generally, the reaction occurred smoothly to afford N,N-disubstituted hydroxylamines (**1.12a-d**) in high yields. In a typical case, the yield of N,N-dibenzylhydroxylamine (**1.12a**) was 60% by the literature method [63JOC1068], but was 93% by the new method.

Table 1.1 Preparation of Symmetrical Secondary Amines and Tertiary Amines, and N,N-Disubstituted Hydroxylamines

Compd	Structure	Reagent	Yield(%)
1.8a	$(C_6H_5CH_2)_2NH$	C_6H_5MgBr	75
1.8b	$[C_6H_5(CH_2)_2]_2NH$	$C_6H_5CH_2MgBr$	95
1.8c	$[CH_3(CH_2)_3CH_2]_2NH$	$CH_3(CH_2)_3MgBr$	65
1.10a	$[(CH_3)_2CHCH_2]_2NCH_3$	$(CH_3)_2CHMgBr$	66
1.10b	$(C_6H_5CH_2)_2NCH_3$	C_6H_5MgBr	90
1.10c	$[(CH_3)_2CHCH_2]_2NC_8H_{17}$-n	$(CH_3)_2CHMgBr$	88
1.10d	$(n\text{-}C_8H_{17}CH_2)_2NC_8H_{17}$-n	$n\text{-}C_8H_{17}MgBr$	95
1.12a	$(C_6H_5CH_2)_2NOH$	C_6H_5MgBr	93
1.12b	$[CH_3(CH_2)_3CH_2]_2NOH$	$CH_3(CH_2)_3MgBr$	89
1.12c	$(n\text{-}C_8H_{17}CH_2)_2NOH$	$n\text{-}C_8H_{17}MgBr$	92
1.12d	$(C_6H_{11}CH_2)_2NOH$	$C_6H_{11}MgCl$	86
1.12e	$(C_6H_5C{\equiv}CCH_2)_2NOH$	$C_6H_5C{\equiv}CLi$	87

It was also found that the reaction of (**1.11**) with lithium phenylacetylide, which was readily prepared from phenylacetylene and butyllithium, took place smoothly and afforded the corresponding dipropargylhydroxylamine (**1.12e**) in high yield.

Table 1.1 shows that the secondary amines, tertiary amines and N,N-disubstituted hydroxylamines were generally obtained in high yields. The diversity in the structures of the products is also reflected in Table 1.1, in which various groups including aliphatic and aromatic, simple and sterically crowded, short and long chain, and even propargyl were introduced.

All the products were characterized by their ^{1}H- and ^{13}C-NMR spectra, elemental analysis data or mass spectra, as well as by comparison of the appropriate physical properties with literature data. The carbon-13 chemical shifts of the CH_2 groups adjacent to the amine nitrogens in the products are generally in the ranges 50-55 ppm for secondary amines, 55-70 ppm for tertiary amines and 60-70 ppm for hydroxylamines (except **1.12e** which is at 49 ppm).

1.3 Conclusions

The work described in this chapter further demonstrates the synthetic utility of benzotriazole derivatives in alkylation reactions with various nucleophiles, leading to the preparation of various secondary and tertiary amines, as well as N,N-disubstituted hydroxylamines. The present methods possess many advantages over the previously existing

literature methods, including simplicity of procedures, easily available starting materials, and yields usually better than those previously reported. Benzotriazole acts as both an activating agent and a leaving group and can be recycled after reaction, thereby making the method economically feasible for large scale production.

1.4 Experimental

1.4.1 General

Melting points were determined on a hot stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian XL-200 spectrometer, using tetramethylsilane (TMS) (δ = 0.00 ppm) as internal reference. ^{13}C-NMR spectra were recorded either on JEOL FX-100 (25 MHz), or Varian XL-200 (50 MHz) instruments as solution either in deuterochloroform ($CDCl_3$) or in deuterodimethyl sulfoxide (DMSO-d_6), using the solvent signals (for $CDCl_3$, δ = 77.00 ppm; for DMSO-d_6, δ = 39.50 ppm) as references.

Exact mass spectra were recorded on a KRATOS MS-80-RFA double focusing spectrometer using the peak matching technique at a nominal resolution of 5,000 (10% valley definition). Combustion analyses were carried out

using a Carlo Erba 1106 elemental analyzer, under the supervision of Dr. R. King at the University of Florida, Department of Chemistry.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were pre-dried over 4Å molecular sieves and distilled under nitrogen from sodium/benzophenone ketyl immediately before use. Silica gel (230-400 mesh) was purchased from Merck.

1.4.2 Preparation of N,N-Bis(benzotriazol-1-ylmethyl)amine (1.7)

Ammonium acetate (3.08 g, 0.04 mol) in water (15 mL) was added to a solution of 1-hydroxymethylbenzotriazole (11.44 g, 0.077 mol) in a mixture of acetonitrile (15 mL) and methanol (10 mL). The mixture was stirred at room temperature for 2 hr during which a white precipitate was formed. The precipitate was filtered, washed with cold water (25 mL) and dried in vacuo (60 °C/30 mm Hg) over P_2O_5 to give N,N-bis(benzotriazol-1-ylmethyl)amine (1.7) (6.65 g, 62% yield). Needles (from 95% ethanol), m.p. 182-184 °C; lit. [87JCS(P1)799] m.p. 177-178 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 7.85-8.12 (m, 4 H, H-4 and H-7), 7.25-7.60 (m, 4 H, H-5 and H-6), 5.72 (d, J = 7.0 Hz, 4 H, $NC\underline{H}_2N$); ^{13}C-NMR (DMSO-d_6) δ 145.3 (C-3a, benzotriazole), 132.1 (C-7a, benzotriazole), 126.7 (C-5 or C-6, benzotriazole), 125.3 (C-6 or C-5, benzotriazole), 118.8 (C-4, benzotriazole), 110.9 (C-7, benzotriazole), 59.9 ($\underline{C}H_2$).

1.4.3 Preparation of N,N-Bis(benzotriazol-1-ylmethyl)-N-alkylamines (1.9)

The preparation of N,N-bis(benzotriazol-1-ylmethyl)-N-alkylamines (1.9) was based on a literature procedure [87JCS(P1)799]. However, improvements were made as specified below.

N,N-Bis(benzotriazol-1-ylmethyl)methylamine (1.9a). Methylamine (6.75 mL, 0.078 mol, 40% water solution) was added to a suspension of 1-hydroxymethylbenzotriazole (22.35 g, 0.15 mol) in diethyl ether (300 mL) and methanol (10 mL). The solution turned homogeneous after stirring for a few min and was left at room temperature overnight. The solvent was evaporated under reduced pressure and the water was removed by repeated distillation with benzene-ethanol. To the residue, diisopropyl ether was added resulting in the formation of a white crystalline solid (15.5 g, 71% yield). Needles (from ethyl acetate and hexane, 50:50, v/v), m.p. 91-93 °C; lit. [87JCS(P1)799] m.p. 88-90 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.3-8.4 (m, 8 H, benzotriazole), 5.71 (s, 4 H, $C\underline{H}_2$), 2.57 (s, 3 H, $C\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 145.9 (C-3a, benzotriazole), 133.2 (C-7a, benzotriazole), 127.8 (C-5 or C-6, benzotriazole), 124.1 (C-6 or C-5, benzotriazole), 119.9 (C-4,

benzotriazole), 109.8 (C-7, benzotriazole), 66.1 ($N\underline{C}H_2N$), 38.4 ($\underline{C}H_3$).

N,N-Bis(benzotriazol-1-ylmethyl)octylamine (**1.9b**). Benzotriazole (11.9 g, 0.1 mol) and octylamine (8.3 mL, 0.05 mol) were stirred in distilled water (100 mL) for a few min, until the organic materials formed a lower liquid phase. Formaldehyde (7.5 mL, 0.1 mol, 37% aqueous solution) was added to the vigorously stirred mixture. After 2 hr the thick suspension was filtered and the white solid was washed with cold water and dried in air to give (**1.9b**) (17.74 g, 91% yield). Needles (from ethanol), m.p. 88-89 °C; lit. [87JCS(P1)799] m.p. 88-89 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 8.10 (d, J = 8.4 Hz, 2 H, H-4), 7.71 (d, J = 8.4 Hz, 2 H, H-7), 7.38-7.55 (m, 4 H, H-5 and H-6), 5.04 (s, 4 H, $NC\underline{H}_2N$), 2.81 (t, J = 7 Hz, 2 H, $NC\underline{H}_2R$), 1.56 (m, 2 H), 1.12-1.24 (m, 10 H), 0.85 (t, J = 7 Hz, 3 H); ^{13}C-NMR ($CDCl_3$) δ 145.9 (C-3a, benzotriazole), 133.1 (C-7a, benzotriazole), 127.7 (C-5 or C-6, benzotriazole), 124.1 (C-6 or C-5, benzotriazole), 119.4 (C-4, benzotriazole), 109.8 (C-7, benzotriazole), 64.4 ($N\underline{C}H_2N$), 50.3 ($N\underline{C}H_2R$), 31.5, 28.9, 27.3, 26.6, 22.5, 13.9, 11.6.

1.4.4 Preparation of Symmetrical Secondary Amines (1.8a-1.8b)

General Procedure. The Grignard reagent was prepared by the standard method from magnesium turnings (0.608 g, 0.025 mol) and the alkyl or aryl halide (0.025 mol) in dry diethyl ether (20 mL). To this solution, a suspension of the benzotriazole derivative (1.7) in dry THF (20 mL) was added dropwise. Immediate frothing and evolution of heat was observed. The mixture was heated under reflux for 1 hr and then poured onto crushed ice (100 g), and stirred with aq. ammonium chloride (20-50 mL) until all the solid dissolved. The organic layer was separated and the aqueous layer was extracted with ether (3 x 40 mL). The combined extracts were washed with 2N NaOH (until TLC showed the absence of benzotriazole) and water (2 x 20 mL) and dried over sodium sulfate (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the crude product which was then purified as described for each particular compound.

Dibenzylamine (1.8a). A pale yellow oil (75%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v). The ^{13}C-NMR spectrum of the product is identical to the standard spectrum (available from the Sadtler Standard Spectra,

Sadtler Research Laboratories, vol. 10, No. 1878). ^{1}H-NMR (DMSO-d_6, TMS) δ 7.15-7.45 (m, 10 H, phenyl protons), 3.68 (d, J = 7 Hz, 4 H, $C\underline{H}_2$), 3.21 (b, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 140.8 (C-ipso), 128.0 (C-o), 127.9 (C-m), 126.5 (C-p), 52.2 ($Ph\underline{C}H_2N$).

2,2'-Diphenylethylamine (1.8b). A clean oil (95%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v). The ^{13}C-NMR spectrum of the product is identical to the standard spectrum (available from the Sadtler Standard Spectra, Sadtler Research Laboratories, vol. 1, No. 67). Lit. [76TL763] b.p. 195 °C/18 mmHg; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.21-7.48 (m, 10 H, phenyl protons), 2.98 (m, 4 H, CH_2N), 2.72 (t, J = 6 Hz, 4 H, $PhCH_2$); ^{13}C-NMR ($CDCl_3$) δ 139.5 (C-ipso), 128.6 (C-o), 128.4 (C-m), 126.2 (C-p), 50.6 ($\underline{C}H_2N$), 35.7 ($Ph\underline{C}H_2$).

Dipentylamine (1.8c). A clean oily liquid (65%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v), b.p. 200-203 °C; lit. b.p. 202-203 °C (commercially available from Aldrich Chemical Company); ^{1}H-NMR ($CDCl_3$, TMS) δ 2.38-2.45 (t, J = 7 Hz, 4 H, CH_2N), 1.18-1.52 (m, 14 H), 0.87 (t, J = 6 Hz, 6 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 54.8 ($\underline{C}H_2N$), 30.5, 27.3, 23.3, 14.6 ($\underline{C}H_3$).

1.4.5 Preparation of Tertiary Amines (**1.10a-1.10d**)

General Procedure. The Grignard reagent was prepared by the standard method from magnesium turnings (0.608 g, 0.025 mol) and the alkyl or aryl halide (0.025 mol) in dry diethyl ether (20 mL). To this solution, the benzotriazole derivatives (**1.9a-1.9b**) (0.01 mol) in dry THF (20 mL) were added dropwise over 15-20 min. The reaction occurred instantaneously with solution frothing and evolution of heat. The reaction mixture was heated under reflux for another 1 hr and then cooled to room temperature. The mixture was poured into ice-water (200 mL) and stirred with aq. ammonium chloride (20-50 mL) until all the solid dissolved. The organic layer was then separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic extracts were subsequently washed with 2 N NaOH (2 x 15 mL) and water (2 x 15 mL) and dried with magnesium sulfate ($MgSO_4$). Evaporation of the solvent afforded the crude product which was purified if necessary as described below.

N-Methyl-N,N-diisobutylamine (**1.10a**). A clean pale yellow oil (66%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v), b.p 141-142 °C; lit [51JOC1911] b.p. 143 °C; ^{1}H-NMR

($CDCl_3$, TMS) δ 2.34 (s, 3 H, NCH_3), 2.23 (d, J = 7 Hz, 4 H, CH_2N), 1.97 (m, 2 H, CH), 1.11 (d, J = 7 Hz, 6 H, $C-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 66.4 ($\underline{C}H_2N$), 42.3 ($N\underline{C}H_3$), 25.6 ($\underline{C}H$), 20.0 ($C-\underline{C}H_3$).

N-Methyl-N,N-dibenzylamine (1.10b). The product was obtained as a very clean (≥ 98% as shown by its NMR spectra) pale yellow oil (90%) without further purification. Its ^{13}C-NMR spectrum is identical to the standard spectrum (available from the Sadtler Standard Spectra, Sadtler Research Laboratories, vol. 10, No. 1881). ^1H-NMR ($CDCl_3$, TMS) δ 7.11-7.43 (m, 10 H, phenyl protons), 3.43 (s, 4 H, CH_2N), 2.09 (s, 3 H, NCH_3); ^{13}C-NMR ($CDCl_3$) δ 138.8 (C-ipso), 128.5 (C-o), 127.8 (C-m), 126.5 (C-p), 61.4 ($\underline{C}H_2N$), 41.7 ($\underline{C}H_3N$).

N-Octyl-N,N-diisobutylamine (1.10c). The product was obtained as a very clean (≥ 98% as shown by its NMR spectra) pale yellow oil (88%). ^1H-NMR ($CDCl_3$, TMS) δ 2.29 (t, J = 7.2 Hz, 2 H, CH_2N), 2.04 (d, J = 7.2 Hz, 4 H, $NC\underline{H}_2CH$), 1.65 (m, 2 H, CH), 1.19-1.35 (m, 12 H), 0.85-0.91 (m, 15 H, $C\underline{H}_3CH$ and $C\underline{H}_3CH_2$); ^{13}C-NMR ($CDCl_3$) δ 64.9 ($N\underline{C}H_2CH$), 56.1 (NCH_2CH), 32.7, 30.4, 30.2, 28.3, 28.2, 27.5, 23.4, 21.7, 14.8. MS (HR) for $C_{16}H_{35}N$ calcd: 241.2768; found: 241.2769.

N-Octyl-N,N-dinonylamine (**1.10d**). The product was obtained as a very clean (≥ 97% as shown by its NMR spectra) pale yellow oil (95%) after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v). ^{1}H-NMR ($CDCl_3$, TMS) δ 2.39 (t, J = 7.2 Hz, 6 H, NCH_2), 1.14-1.45 (m, 40 H), 0.88 (t, J = 7.2 Hz, 9 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 55.2 ($\underline{C}H_2N$), 33.0, 30.7, 30.4, 28.6, 28.5, 28.3, 23.7, 14.9. MS (HR) for $C_{26}H_{55}N$ calcd: 381.4331; found: 381.4314.

1.4.6 Preparation of N,N-Disubstituted Hydroxylamines (**1.12a-1.12e**)

General Procedure. The procedure for the preparation of N,N-disubstituted hydroxylamines (**1.12a-1.12e**) was similar to the procedure for the preparation of symmetrical secondary amines (**1.8a-1.8c**), except in the case of (1.12e) for which the procedure was described below. The purification of the crude product was described below for the particular compound.

N,N-Dibenzylhydroxylamine (**1.12a**). The product was obtained as needles (94%) by recrystallization from 85% ethanol, m.p. 121-123 °C; lit [19JA673] m.p. 123 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 7.82 (s, 1 H, NOH), 7.21-7.42 (m, 10 H, phenyl protons), 3.79 (s, 4 H, CH_2N); ^{13}C-NMR

(DMSO-d_6) δ 138.5 (C-ipso), 128.9 (C-o), 127.9 (C-m), 126.7 (C-p), 63.7 ($\underline{C}H_2N$).

N,N-Dipentylhydroxylamine (**1.12b**). The product was obtained as plates (89%) by recrystallization from 85% methanol, m.p. 56-57 °C; lit. [57JA964] m.p. 57-58 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 2.62 (t, J = 7.2 Hz, 4 H, CH_2N), 1.58 (m, 4 H, $C\underline{H}_2CH_2N$), 1.19-1.38 (m, 8 H), 0.92 (t, J = 7.2 Hz, 6 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 60.0 ($\underline{C}H_2N$), 28.9 26.2, 21.9, 13.4 ($\underline{C}H_3$).

N,N-Dinonylhydroxylamine (**1.12c**). The product was obtained as needles (92%) by recrystallization from hexanes, m.p. 76-78 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 2.62 (t, J = 6.8 Hz, 4 H, CH_2N), 1.18-1.60 (m, 28 H), 0.89 (t, J = 7.2 Hz, 6 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 60.9 ($\underline{C}H_2N$), 31.9, 29.7, 29.6, 29.3, 27.5, 27.3, 22.7, 14.1.

Anal. Calcd for $C_{18}H_{39}NO$: C, 75.72; H, 13.77; N, 4.91. Found: C, 75.43; H, 13.98; N, 4.54.

N,N-Dicyclohexylmethylhydroxylamine (**1.12d**). The product was obtained as needles (86%) by recrystallization from 85% ethanol, m.p. 69-71 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 2.48 (d, J = 7 Hz, 4 H, CH_2N), 0.78-1.89 (m, 22 H,

cyclohexyl); ^{13}C-NMR ($CDCl_3$) δ 67.1 ($\underline{C}H_2N$), 34.9 34.1, 26.0, 25.4.

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.22. Found: C, 74.49; H, 12.19; N, 5.96.

N,N-Di(3-phenylprop-2-ynyl)hydroxylamine (**1.12e**). To the solution of phenylacetylene (1.02 g, 0.01 mol) in dry THF (30 mL), butyllithium (4.4 mL, 0.011 mol, 2.5 M in diethyl ether) was added dropwise under nitrogen at -78 °C. After the addition, the mixture was allowed to warm to room temperature and stirred for another 2 hr. To this solution, the benzotriazole derivative (**1.11**) (0.89 g, 0.003 mol) was added over 15 min at room temperature. The reaction mixture was stirred for 1 hr, poured into ice-water (100 mL) and stirred with aq. ammonium chloride (15 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 20 mL). The combined extracts were washed with 2N NaOH (2 x 15 mL), water (2 x 15 mL) and dried with magnesium sulfate. After evaporation of the solvent, a semi-solid was obtained. The pure compound was obtained as needles by recrystallization from ethyl acetate and ligroin (90:10, v/v), m.p. 94-95 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.44-7.49 (m, 4 H, phenyl protons), 7.28-7.32 (m, 6 H, phenyl protons), 6.58 (bs, 1 H, OH), 3.99 (s, 4 H, CH_2N); ^{13}C-NMR ($CDCl_3$) δ

131.8 (C-o), 128.4 (C-m), 128.3 (C-p), 122.7 (C-ipso), 85.6 (Ph$\underline{C}$≡C), 83.3 (C≡$\underline{C}$CH$_2$), 49.0 ($\underline{C}$H$_2$N).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.71; H, 5.77; N, 4.99.

CHAPTER II

α-LITHIATION OF PYRAZOLES

2.1 Introduction

In a heterocycle which contains an NH group, the inductive electron-withdrawing effect of the nitrogen atom generates a considerable positive charge on the adjacent carbon, greatly increasing the acidity of the α-hydrogen. As a result, the generation of an α-carbanion becomes feasible and subsequent electrophilic substitution at the α-carbon is possible. However, in practice, attempted lithiation of such heterocycles normally only leads to the N-lithio species. Since the proton at nitrogen is much more acidic than the protons at the α-carbons, its removal occurs prior to the abstraction of the α-carbon proton. The resultant nitrogen anion, having a negative charge, would exert a strong repulsion on the α-carbanion, if formed, thus leading to the destabilization of such an α-carbanion. Hence, in almost every case, prior protection of the NH group is essential for the successful α-lithiation of such heterocycles. Furthermore, even when the NH group has been protected, the α-carbanion, once

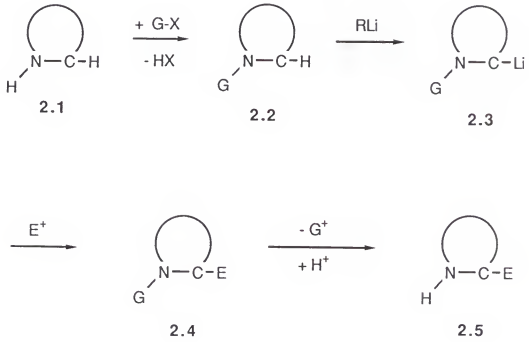
generated, is destablized by the adjacent nitrogen atom which still contains a lone-pair of electrons.

Chemical transformations involving lithiation and subsequent electrophilic substitution on α-carbons of heterocycles is a long term interest from both the mechanistic and synthetic points of view. The most challenging part is the generation of α-carbanions. The direct approach towards α-carbanions of heterocycles containing NH groups can be achieved by two routes, the "protection" route and the "protection-activation" route. Over the last decade much effort has been devoted to the generation of α-carbanions and accordingly, the fashioning of efficient protecting and activating groups has been intensively investigated. Several reviews have appeared on these and related topics [79OR(26)1, 85MI1, 88PIA187].

2.1.1 Generation of α-Carbanions by the Protection Route

In the protection route, the NH group of a heterocycle is first masked with a protecting group and the subsequent abstraction of a proton at the α-carbon can be achieved using a strong lithiating agent. The groups used here are only for the prior protection of the NH group and are not functionalized to provide activation towards the abstraction of α-protons. Scheme 2.1 illustrates the sequence of such an approach. A group "G"

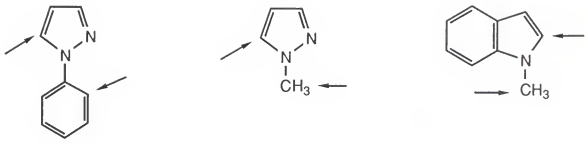
is added to the heterocycle (**2.1**) which contains a NH group to afford the derivative (**2.2**). Subsequent removal of a proton (either attached to an sp^2 or to an sp^3 carbon) adjacent to the nitrogen of (**2.2**) gives (**2.3**) which is then allowed to react with an electrophile to give the substituted derivative (**2.4**). Subsequent removal of G from (**2.4**) provides the α-substituted heterocycle (**2.5**). In this sequence the introduction of the protecting group G is essential and the formation of (**2.3**), an α-lithio species, by deprotonation of (**2.2**) is the novel step.



2.1 **2.2** **2.3** **2.4** **2.5**

Scheme 2.1

Alkyl and aryl groups are frequently employed as protecting groups since they can be easily introduced. The lithiation of such N-alkyl and N-aryl heterocycles usually generates α-carbanions easily. For example, while pyrrole undergoes deprotonation only at the NH group even with excess butyllithium, N-methyl- and N-phenylpyrrole undergo α-lithiation easily to give the corresponding α-carbanions [55JOC225]. Similarly, many heterocycles such as indoles, pyrazoles, imidazoles, triazoles and tetrazoles, undergo successful α-lithiation when the hydrogen of their NH groups is substituted by an alkyl or aryl group. However, the use of these protecting groups has several associated problems. Firstly, their lack of activation towards the abstraction of α-protons results in slower rates of lithiation and therefore, higher temperatures and longer reaction times are needed. In order to overcome this problem, additives such as tetramethylethylenediamine (TMEDA) are frequently used. However, this causes the additional problem of removing such additives during workup. Secondly, the kinetic acidity of the protons of alkyl and aryl groups are usually high enough to compete simultaneously with lithiation in the heterocyclic rings [58JA6271, 72JOC215, 83T2023, 84JCS(P1)481] (Figure 2.1). Thirdly, the removal of alkyl and aryl groups is generally not facile and harsh reaction conditions are needed [74JOC940, 75LA1264, 86JHC1257].



2.6 2.7 2.8

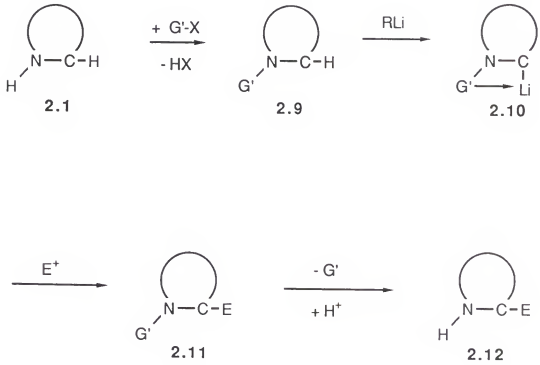
Figure 2.1 Competing Lithiation between Heterocyclic Rings and Protecting Groups

From a synthetic point of view, the use of alkyl and aryl groups as protecting groups is not satisfactory and hence alternatives must be sought.

2.1.2 Generation of α-Carbanions by the Protection-Activation Route

In the protection-activation route, the nature of the groups chosen is different from those used in the protection route. The groups used here are capable of performing two functions simultaneously. Firstly, the more acidic proton of the NH group is protected from reacting with the lithiating agent. Secondly, and most importantly, they play a major role in activating the α-position towards proton abstraction. This process of α-activation

is necessary for two reasons: (i) the α-hydrogens of heterocycles having NH groups are not acidic enough to be abstracted by strong bases; (ii) the carbanions formed are not stable enough due to the repulsion by the adjacent nitrogen lone-pair electrons. Scheme 2.2 shows the process involving a "protecting-activating" group "G'" towards the α-lithiation of a heterocycle.

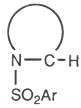


Scheme 2.2

The key step in the sequence in Scheme 2.2 is the formation of the α-lithio species (**2.10**) from (**2.9**), since it involves the process of activation. There are several ways by which the protecting group (in **2.9**) could activate the α-positions. According to Beak [84CRV471], prior complexation with lithium, dipole stabilization, and/or resonance delocalization are the three major contributions from group G' to the activation of the α-position by stabilization of the intermediate (**2.10**).

In addition to this, the group G', in order to be synthetically useful, should not contain any acidic hydrogens, should be stable towards the lithiating agent, and should be easily introduced and removed under mild conditions.

Based on these concepts, a number of protecting-activating groups which are useful in the sequence shown in Scheme 2.2 have been developed in recent years. Some of the versatile and frequently used "protecting-activating" groups are shown in Figure 2.2. All these (except SiR_3 groups) bear a heteroatom which can facilitate the α-lithiation and simultaneously stabilize the α-carbanion through complexation with lithium. A more comprehensive picture can be obtained from Gschwend's review [79OR(26)1] and from related references [84JCS(P1)481, 88JOC1107].



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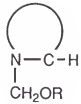

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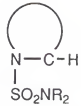

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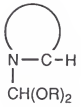

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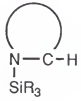


2.17

Figure 2.2 Protecting-activating Groups Previously Reported in the Literature

Arylsulfonyl groups (**2.13**) can be easily introduced and removed, and α-lithiation can be facilitated with these groups in many cases [79OR(26)1]. However, with imidazoles, they appear to reduce the ease of lithiation at α-position and thus harsh reaction conditions are required.

Alkoxymethyl groups (**2.14**) have been abundantly employed as "protecting-activating" groups since they facilitate the α-lithiation by strong complexation with lithium agent. High yields of α-lithiations can be obtained in most cases. Unfortunately, a significant

disadvantage of alkoxymethyl groups is the severe deprotection conditions required and accordingly, comparatively low isolated yields of some of the products were observed [78JA3918].

Sulfonamides (**2.15**) initially appeared to be among the best protecting groups available [84JCS(P1)481, 86T2351], but recent work has shown that the lithio derivatives fail to react with electrophiles such as dimethylformamide (DMF) [88JOC1107].

Trialkylsilyl groups (**2.17**) have their own merits in that the starting materials are commercially available and can be easily introduced and removed. However, they are unsuitable for a number of heterocyclic systems because of their facile rearrangement from the protected nitrogen atom to the α-carbon atom during the lithiation [82JCS-(P1)1833].

2.1.3 Carbon Dioxide, Aminals and Hemiaminals as "Protecting-Activating" Groups

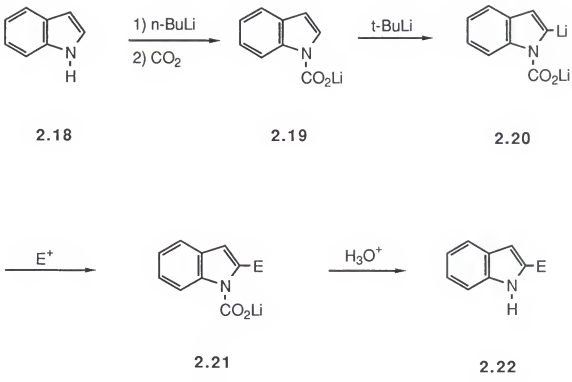
Amides and carbamates are commonly used to protect NH groups, but they are not practical in carbanionic systems because of their great susceptibility to nucleophilic attack. This problem can be partly overcome by the use of more hindered derivatives, but then they usually require much harsher conditions for their removal. Recently, Katritzky et al. have found a successful solution to both

of these problems. The use of readily available and relatively non-toxic carbon dioxide (CO_2) leads to the successful protection of NH groups in a number of heterocycles as their carbamate anion derivatives. Because of the presence of the negative charge, these carbamates are much more resistant to nucleophilic displacement, but after protonation, they readily undergo decarboxylation on gentle warming to restore the NH functionality [87H1333, 87MI1].

As just described, α-chemical transformations of heterocycles containing NH groups can be achieved in a three-step sequence: protection, α-lithiation and electrophilic addition and finally deprotection (Scheme 2.2). The use of carbon dioxide as protecting-activating group was also implemented in the same manner.

The initial investigation carried out by Katritzky and coworkers was focussed on indole, and a successful one-pot method for the preparation of 2-substituted indole derivatives was achieved [85TL5935]. Indole (**2.18**) was first converted into its lithium carbamate (**2.19**) by treatment with butyllithium in tetrahydrofuran, followed by addition of carbon dioxide. Lithiation of this lithium carbamate at the α-position was then accomplished with 1.2 equivalents of t-butyllithium in the same solvent at -20 °C to give (**2.20**), which was then trapped with various

electrophiles to provide the α-substituted carbamates (2.21) (Scheme 2.3). The latter, without isolation, were readily deprotected under acidic workup to give the 2-substituted indoles (2.22) in good yields.



2.18 2.19 2.20

2.21 2.22

Scheme 2.3

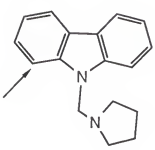
The carbon dioxide protocol has been successfully extended to other heterocycles including pyrrole [88OPP585], tetrahydroisoquinoline [86T2571], tetrahydroquinoline [89JCS(P1)17], indoline [89JCS(P1)17], thiazolidine [89JCS(P1)17], phenothiazine [88S215] and phenoxazine [87H3135] [in these cases, lithiation occurred

at the adjacent (C-1) aromatic carbon]. In all cases, good to excellent yields were obtained and reactions were all carried out in one-pot sequences.

Although the carbon dioxide method is clearly a powerful strategy for protecting and activating, it has its definite limitations. Thus it failed in a number of attempted applications, such as with imidazole, benzimidazole, pyrazole and carbazole. These failures are due to several reasons. The main reason is, perhaps, the reduced solubility of the lithium carbamates of these heterocycles in organic solvents such as ethyl ether and tetrahydrofuran, which results in incomplete α-lithiation. Furthermore, the partial cleavage of the carbamate moiety was also observed during the α-lithiation of several heterocycles.

In searching for an alternative protecting-activating system for heterocycles with which the carbon dioxide method failed, N-(dialkylamino)methyl (aminal) groups were chosen for investigation by previous workers of this group. The directing effect of dialkylaminomethyl groups in carbocyclic chemistry is well known [79CRV287, 79OR(26)1, 87MI2, 87MI3], thus their extension to heterocyclic systems is promising. Formation of the aminal intermediates is simply achieved by reaction of the heterocycles with the appropriate secondary amines and formaldehyde under standard Mannich conditions. Indeed,

the directing and activating effects of aminal groups in α-lithiations were found to be powerful in several heterocyclic systems, as shown in Figure 2.3 [88JOC794, 88JOC5685].



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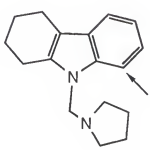

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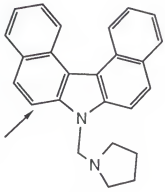

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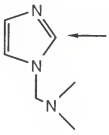

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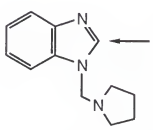

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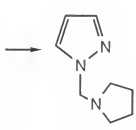


2.28

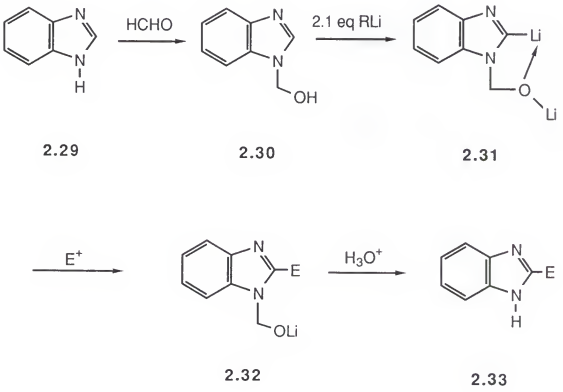
Figure 2.3 Aminals as Protecting-activating Groups in the Lithiation of Number of Heterocyclic Systems

In all these cases, the aminal groups can stabilize the α-carbanions by chelating the lithium with the amino nitrogen atom through either a six-membered or a five-membered ring whichever is thermodynamically favorable. The α-lithiation occurs predominantly at the more kinetically acidic positions such as C-8 in 1,2,3,4-tetrahydrocarbazole (**2.24**), C-2 in imidazole (**2.26**) and in benzimidazole (**2.27**), as well as C-5 in pyrazole (**2.28**). In addition, the aminal groups were easily removed on gentle warming with dilute acid whereas the other functionalities introduced remained intact under these conditions.

As a rational extension of the aminal system, the potential merits of hemiaminal anions (α-amino alkoxides) as protecting-activating groups were next investigated by previous workers in this group. The utility of α-amino alkoxides in aromatic lithiations [79OR(26)1, 87MI2], and their role as *in situ* aldehyde protecting groups [68ACS1358, 84JOC1078] is well known, but their ability to assist in lithiation of nitrogen-containing heterocycles had not been investigated. The closest analogy could be found in the lithiation of N-protected heterocyclic aldehydes *via* their α-amino alkoxides [87JOC104].

Hemiaminals derived from aldehydes and ketones are usually very unstable, but when an electron-withdrawing group is attached to the nitrogen atom they are sometimes

stable enough to isolate. Some heterocyclic examples are those derived from benzotriazole, which have been particularly well investigated [87JCS(P1)791], phthalimide [47JA254] and succinimide [63ZPC1]. Irrespective of the unfavorable equilibrium in hemiaminal formation, it was envisaged that a heterocycle derived lithium hemiaminal could potentially serve as a protecting-activating group during the α-lithiation of the heterocycle. Particularly attractive seemed the possible exploitation of the above mentioned unfavorable equilibrium to facilitate the deprotection of the heterocycle.



Scheme 2.4

In a preliminary investigation by Katritzky and Akutagawa, benzimidazole was selected as the heterocycle to investigate. The hemiaminal derivative (**2.30**) was readily prepared by the reaction of benzimidazole (**2.29**) with formaldehyde. The α-lithiation of (**2.30**) was successfully achieved by treatment with 2.1 equivalents of an organolithium reagent (butyllithium, t-butyllithium, or LDA). The lithium species (**2.31**), after being trapped with a variety of electrophiles, afforded the 2-substituted hemiaminal anions (**2.32**). The latter, without the need of isolation, were readily deprotected during acidic workup to provide the 2-substituted benzimidazoles (**2.33**) in moderate to good yields (Scheme 2.4) [89JOC2949]. Again, the whole set of operations was implemented in one-pot.

These definite results suggested that both aminal and hemiaminal methods could be further applied to the α-lithiation of other heterocyclic systems. Therefore a detailed study of these novel α-lithiation processes was most desirable.

2.1.4 Aim of the Work

The aim of the present work was to further explore the potential use of the hemiaminal protecting-activating method in the α-lithiation of NH containing heterocycles, particularly in those cases where the carbon dioxide

method failed. The heterocycle chosen for the study was pyrazole since the α-lithiation of this azole had been less studied than that of other azoles (e.g. benzimidazole, imidazole).

N-Unsubstituted pyrazoles have been reported to undergo lithiation at the 5-position, but the yields of subsequent reactions with electrophiles were poor: e.g. with phenyllithium or butyllithium, followed by electrophilic attack with carbon dioxide, pyrazole gave only 7% and 9% of pyrazole-3-carboxylic acid, respectively [59LA55]. 1-Methylpyrazole can be lithiated at the 5-position to give 5-substituted 1-methylpyrazoles [58JA6271]. However, 1-phenylpyrazole undergoes lithiation competitively at the pyrazole 5-position and at the ortho position of the phenyl ring, in a 4:1 ratio [58JA6271]. Previous work [83T2023] by Katritzky and coworkers has confirmed that lithiation of 1-methylpyrazoles occurs in the methyl group of 1-methylpyrazole itself, as well as in its analogues blocked at the C-3 and C-5 positions. Similar results had been reported previously [72JOC215]. Recently Micetich et al. [85H943] reported that with careful control of the reaction conditions exclusive lithiation at the C-5 position of 1-phenylpyrazole can be achieved. But removal of the phenyl group requires very harsh conditions such as reductive elimination in liquid ammonia or high pressure hydrogenation. Clearly, neither

methyl nor phenyl are suitable as protecting groups for pyrazole because of the above limitations.

While the benzyl group is often used to protect the NH of heterocycles, it is unsatisfactory for pyrazole since competitive lithiation at the benzylic methylene group is observed [84JCS(P1)481]. A systematic study by Katritzky and coworkers [83T2023] showed that 1-benzylpyrazole is metallated at the CH_2 group under kinetic control at low temperature and that the metalloorganic intermediate could rearrange at room temperature to give the thermodynamically more stable 5-lithio-1-benzylpyrazole. Katritzky and coworkers have also shown that gem-bis(pyrazol-1-yl)alkanes can be lithiated both at the inter-ring carbon atom and at the 5-position of the ring [83T4133].

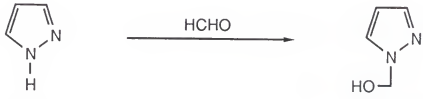
As just described, the carbon dioxide method which has been successfully used as an NH protecting group for the lithiation of indoles and other nitrogen heterocycles, failed for pyrazole. The N-(dialkylaminomethyl) protection has been successfully applied for the α-lithiation of imidazole, benzimidazole and pyrazole. Overall yields of 45%-78% of 5-substituted pyrazoles were achieved. However, its disadvantage is the need to isolate and purify the N-(dialkylaminomethyl)pyrazole before the main reaction.

The use of tetrahydropyranyl, apparently allows metallation of pyrazole under mild conditions and gives good yields of the 5-substituted pyrazoles, but unfortunately, no experimental details have been given [79OR(26)1].

In view of the easy introduction and removal of the hemiaminal group, α-lithiation of the pyrazole via its hemiaminal derivative appears as a potentially superior method over the existing ones.

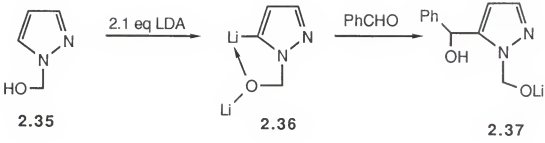
2.2 Results and Discussion

The preparation of N-hydroxymethylpyrazole (**2.35**) (Scheme 2.5) was readily accomplished by treatment of pyrazole (**2.34**) with aqueous formaldehyde utilizing a previously reported procedure [52CB820, 69BSF2064]. After recrystallization, a 65% yield of the pure compound was obtained.



2.34 **2.35**

Scheme 2.5



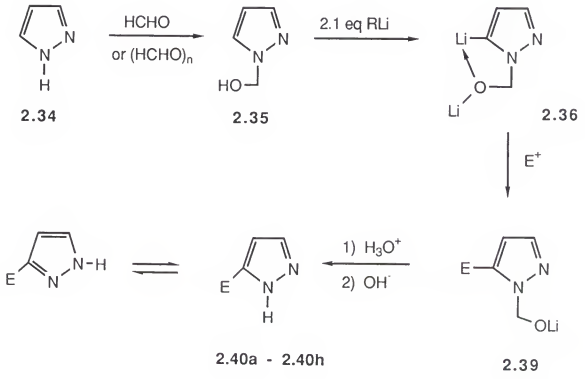
2.35 **2.36** **2.37**

2.38

Scheme 2.6

The initial investigation of the α-lithiation of N-hydroxymethylpyrazole (**2.35**) was carried out in tetrahydrofuran at low temperature (Scheme 2.6). Treatment of (**2.35**) first with one equivalent of lithium diisopropylamide (LDA) at -78 °C gave a heavy white precipitate indicating the formation of the lithium salt of the hemiaminal. After addition of a further 1.1 equivalents of LDA at the same temperature, the color of the suspension gradually changed to yellow. In order to complete the lithiation, the reaction mixture was then allowed to warm

to -20 °C and kept at that temperature for an additional hour. After recooling to -78 °C, 1.1 equivalents of benzaldehyde was added to the solution and the color of the suspension turned pale green. The mixture was stirred at -78 °C for 4 hours (ca.) and then allowed to warm to room temperature and stirred overnight. The deprotection of the hemiaminal was accomplished by extraction with 2N aqueous hydrochloric acid. After the neutralization of the acidic extracts, a white precipitate was formed which was identified as 3(5)-phenylhydroxymethylpyrazole (**2.38**) in an overall yield of 47%.



Scheme 2.7

This successful reaction led to an extensive investigation of the lithiation of hemiaminal (2.35) with a variety of electrophiles. Similar to the previous report on benzimidazole, the reaction sequence was then carried out in a one-pot procedure which consisted of three stages: protection, main reaction (lithiation and substitution), and work-up including deprotection. Indeed, the protecting group was readily introduced by the reaction of pyrazole (2.34) with paraformaldehyde in tetrahydrofuran at 40 °C (Scheme 2.7). Using paraformaldehyde has the advantage that the subsequent operations can be directly carried out without the need to purify the N-hydroxymethylpyrazole (2.35). This is not the case when aqueous formaldehyde is used where the intermediate N-hydroxymethylpyrazole needs to be dried prior to the main reaction. A clean homogeneous solution forms indicating complete formation of (2.35). Similarly, lithiation was accomplished at -78 °C to -20 °C by treatment of (2.35) with 2.1 equivalents of a lithiating agent. It was found that butyllithium, t-butyllithium, and LDA, all produced the dilithiated pyrazole (2.36) smoothly at -20 °C in less than 1 hour. The lithio species (2.36) was then quenched with various electrophiles at -78 °C; warming the solution to 20 °C then gave the expected 5-substituted 1-lithioxymethylpyrazole (2.39). The electrophiles employed included aldehydes (C_6H_5CHO, $p\text{-}CH_3C_6H_5CHO$), ketones [$(C_6H_5)_2CO$, cyclohexanone], an

organohalide ($C_6H_5CH_2Br$), disulfides [$(C_6H_5S)_2$, $(C_6H_5CH_2S)_2$], and an isocyanate (C_6H_5NCO).

Deprotection was readily accomplished by the acid-catalyzed hydrolysis of the resulting (**2.39**). The reaction mixture was quenched with aqueous ammonium chloride and diluted with diethyl ether, followed by extraction with dilute hydrochloric acid. Neutralization of the acidic extracts with aqueous ammonium hydroxide provided the 3(5)-substituted pyrazoles (**2.40**). The deprotection is also effected by the silica gel assisted fission of the hydroxymethyl group. Thus the residue, after evaporation of the organic solvent, was passed through a silica gel column to give the deprotected product. Under both sets of conditions, the 3(5)-substituted pyrazoles (**2.40a-h**) were obtained in acceptable overall yields based on pyrazole (**2.34**).

Table 2.1 gives the results of applying this method to a variety of electrophiles. Substituents introduced include alkyls and alkylsulfides, carbinals and carbamates.

In comparison with other protection and activation methods, the present one-pot hemiaminal method for 5-functionalization of pyrazole has the following advantages:

1. The protecting group is readily introduced under mild conditions using readily available reagents. No intermediate purification step is needed when paraform-aldehyde is used.

Table 2.1. Preparation of N-Unsubstituted-5(3)-Substituted Pyrazoles

Compds	CH_2O Source	Lithiating Agent	Electrophile	Yield[b] (%)	mp (°C)	Molecular Formula	Calcd (found) C	H	N
2.40a	CH_2O/H_2O[a]	LDA	C_6H_5CHO	47[c]	113-114	$C_{10}H_{10}N_2O$	-		
2.40a	CH_2O/H_2O	LDA	C_6H_5CHO	44[c]	113-114	-	-		
2.40a	$(CH_2O)_n$	t-BuLi	C_6H_5CHO	53[c]	113-114	-	-		
2.40a	$(CH_2O)_n$	BuLi	C_6H_5CHO	37[c]	113-114	-	-		
2.40b	$(CH_2O)_n$	t-BuLi	$4\text{-}CH_3C_6H_4CHO$	45[c]	96-97	$C_{11}H_{12}N_2O$	70.19	6.43	14.86
							(70.23)	(6.43)	(14.99)
2.40c	$(CH_2O)_n$	t-BuLi	$(C_6H_5S)_2$	53[d]	oil	$C_9H_8N_2S$	61.34	4.58	15.90
							(61.53)	(4.59)	(15.61)
2.40d	$(CH_2O)_n$	t-BuLi	$C_6H_5CH_2Br$	54[d]	oil	$C_{10}H_{10}N_2$	-		
2.40e	$(CH_2O)_n$	t-BuLi	$(C_6H_5CH_2S)_2$	76[d]	oil	$C_{10}H_{10}N_2S$	-		
2.40f	$(CH_2O)_n$	t-BuLi	$(C_6H_5)_2CO$	61[d]	121-123	$C_{16}H_{14}N_2O$	76.78	5.64	11.19
							(76.48)	(5.64)	(11.26)
2.40g	$(CH_2O)_n$	t-BuLi	Cyclohexanone	51[d]	122-123	$C_9H_{14}N_2O$	65.03	8.49	16.85
							(64.81)	(8.53)	(16.52)
2.40h	$(CH_2O)_n$	t-BuLi	C_6H_5NCO	56[d]	125-127	$C_{10}H_9N_3O$	64.16	4.85	22.45
							(64.24)	(4.88)	(22.65)

[a] 1-Hydroxymethylpyrazole was used as a starting material. [b] Isolated overall yields of the 5(3)-pyrazoles, based on N-H pyrazole. [c] Deprotected by acid-catalysed dehydroxymethylation using 2N aqueous hydrochloric acid. [d] Deprotected by passing through silica gel column using diethyl ether-hexane (2:1) as first eluent followed by ethyl acetate.

2. A variety of readily available lithiating reagents (butyllithium, t-butyllithium, or LDA) affords the dilithio derivative efficiently under mild conditions, and the anion is sufficiently reactive to attack a range of electrophiles, even the hindered electrophile benzophenone (**2.40f**, Table 2.1).

3. Deprotection is readily accomplished by shaking with aqueous hydrochloric acid or by passing through a silica gel column.

4. The whole procedure is one-pot, with moderate to good overall yields.

All the compounds were characterized by ^{1}H and ^{13}C-NMR spectra and by elemental analyses, in addition to the literature data. The ^{1}H-NMR and ^{13}C-NMR spectral data of the 5(3)-substituted pyrazoles prepared are given in Tables 2.2 and 2.3. The methylene protons of the parent 1-hydroxylmethylpyrazole (**2.35**) appear as a singlet at 5.5 ppm and the clearly distinguishable proton signals of pyrazole H-4, and H-5 together with H-3, appear as multiplets at 6.3 ppm and at 7.6 ppm, respectively. The carbon chemical shift of the CH_2 group appears at 73.4 ppm and the three pyrazole ring carbon signals resonate at 140.3, 106.2 and 129.9 ppm (for C-3, C-4 and C-5 respectively), in good agreement with the literature data [88MRC129].

After reaction, the 5(3)-substituted pyrazoles

(**2.40a-h**) obtained show the loss of the original CH_2 signal at 5.5 ppm (^{1}H-NMR) and the H-4 and H-5 (or H-3) of pyrazole now show clearly as doublets in the 5.80-6.87 ppm region and in the 7.01-7.46 ppm region, respectively, indicating that the substitution with electrophiles has occurred at the azole ring. The coupling constants between the H-4 and the H-5 ring protons are all about 2 Hz, in good accord with the literature [85H943]. The substituted ring carbons of the 5(3)-substituted pyrazoles, except for compound (**2.40g**), are shifted a little downfield at 140.8-146.7 ppm (C-3), 101.9-110.5 ppm (C-4), 130.3-135.7 ppm (C-5) which are in good agreement with the data previously reported [83T4133] as compared to the parent pyrazole.

Compounds (**2.40a-h**) exist in two tautomeric forms (C-3 or C-5 substituted), and in some cases (**2.40f** and **2.40g**), two of the carbon signals (C-3 or C-5) appear as broad peaks at room temperature and gradually become sharp singlets as the temperature is increased to about 50 °C, indicating that the tautomerization between the two forms is slow on the NMR time-scale at room temperature and reaches fast equilibrium at higher temperature. A strong hydrogen bond between the NH and the OH group presumably retards the transposition of the NH proton to the adjacent nitrogen atom.

The proton signals of the NH of the 5(3)-substituted pyrazoles are far more downfield at 12.5-14.1 ppm and usually depend on solvents and concentration.

Table 2.2. ^{1}H-NMR Chemical Shifts (δ) for 5(3)-Substituted Pyrazole Ring Protons (ppm)

Compound	5(3)-substituent	Pyrazole		
		H-4	H-3(H-5)	NH[a]
2.40a	$C_6H_5CH(OH)$	6.08[b]	-[c]	12.7[d]
2.40b	4-$MeC_6H_4CH(OH)$	6.12[b]	-[c]	12.7[d]
2.40c	C_6H_5S	6.38[b]	7.46[b]	12.5[d]
2.40d	$C_6H_5CH_2$	5.92[b]	7.28[b]	12.5[d]
2.40e	$C_6H_5CH_2S$	6.18[b]	7.46[b]	12.7[d]
2.40f	$(C_6H_5)_2C(OH)$	5.80[b]	7.01[b]	14.8[d]
2.40g	$(CH_2)_5COH$	6.12[b]	7.21[b]	-[e]
2.40h	C_6H_5NHCO	6.87[b]	7.12[b]	-[e]

[a] The chemical shift of NH depends on solvents and concentration. [b] Doublet, J = 2 Hz. [c] Pyrazole H-3 or H-5 immersed in the other aromatic protons. [d] Broad singlet. [e] NH signal not observed.

Table 2.3. ^{13}C-NMR Chemical Shifts (δ) for 5(3)-Substituted Pyrazole Ring Carbons (ppm)

Compound	5(3)-Substituent	Pyrazole		
		C-3	C-4	C-5
2.40a	$C_6H_5CH(OH)$	144.2	101.9	135.2
2.40b	4-$MeC_6H_4CH(OH)$	141.6	101.9	135.7
2.40c	C_6H_5S	140.8	110.5	131.7
2.40d	$C_6H_5CH_2$	146.9	103.7	133.3
2.40e	$C_6H_5CH_2S$	146.3	109.2	131.2
2.40f	$(C_6H_5)_2C(OH)$	146.2	105.2	132.2
2.40g	$(CH_2)_5COH$	133.4	100.8	111.2
2.40h	C_6H_5NHCO	146.7	105.6	130.3

2.3. Conclusions

In summary, 5(3)-substituted pyrazoles were synthesized in one-pot sequences in the key step of which a dilithiated hemiaminal was successfully reacted with a variety of electrophiles. The particular ease of introduction and removal which characterize the use of formaldehyde as a protecting group for pyrazole, offers a significant advantage over the N-substituents previously employed for this purpose.

2.4. Experimental

2.4.1 General

Column chromatography was carried out by using MBS silica gel (230-400 mesh). Melting points of the products were measured by a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H-NMR (200 MHz) spectra were recorded on a Varian XL-200 (FT mode) spectrometer, using tetramethylsilane (TMS) (δ = 0.00 ppm) as internal reference. ^{13}C-NMR (50 MHz) were recorded on a Varian XL-200 (FT mode) spectrometer as solutions either in deuterochloroform ($CDCl_3$) or in deuterodimmethylsulfoxide (DMSO-d_6), using solvent signals (for $CDCl_3$, δ = 77.00 ppm; for DMSO-d_6, δ = 39.50 ppm) as references. Combustion analyses were carried out using a Carlo Erba

1106 elemental instrument, under the supervision of Dr. King at the University of Florida, Department of Chemistry.

Commercial pyrazole (Aldrich) was used without purification. Butyllithium and t-butyllithium (Aldrich) were used without further purification. LDA was freshly prepared from N,N-diisopropylamine (dried over calcium hydride and distilled) and butyllithium immediately before each run. Tetrahydrofuran was predried with molecular sieves 4Å and freshly distilled from calcium hydride before use. Formaldehyde (37% aqueous solution, Fisher Scientific Co.) and paraformaldehyde (Fisher Scientific Co.) were used without further purification. Electrophiles were purified by standard methods before use.

1-Hydroxymethylpyrazole (**2.35**) was prepared according to the modified literature procedure, m.p. 86-87 °C, lit. [52CB820] m.p. 88 °C.

2.4.2 Preparation of 5(3)-Substituted Pyrazoles. General Procedure

2.4.2.1 Protection, Method A: Preparation of the hemiaminal using 37% aqueous formaldehyde

Pyrazole (1.00 g, 14.4 mmol) was placed in a two necked flask. Tetrahydrofuran (40 mL) was added at 20 °C to give a clear solution. To this, formaldehyde (1.31 g, 1.0 eq., 37% water solution) was added at 20 °C and

stirred for 4 hr to give a homogeneous solution. The solvent was removed under reduced pressure with a rotary evaporator and the residue was dried in vacuo for 24 hr.

2.4.2.2 Protection, Method B: Preparation of the hemiaminal using paraformaldehyde

Pyrazole (1.00 g, 14.4 mmol) and paraformaldehyde (591 mg, 1.3 eq.) were placed in a two necked flask. The interior of the flask was evacuated and flushed with dry argon three times. Tetrahydrofuran (45 mL) was added to give a suspension. The whole was kept well-stirred at 45 °C for 4 hr to give a homogeneous solution. TLC showed only one spot which corresponded to 1-hydroxymethyl-pyrazole.

2.4.2.3 Main Reaction: Dilithiation of the hemiaminal

The solution obtained from the above reaction was cooled to -78 °C to give a precipitate, and freshly prepared LDA [2.0 eq., from diisopropylamine (4.1 mL) and butyllithium (11.5 mL of 2.5 M hexane solution)] or t-butyllithium (17.8 mL of 1.7 M pentane solution) or butyllithium (11.5 mL of 2.5 M hexane solution) was added slowly at -78 °C. The cooling bath was removed to allow the solution to warm to -20 °C. The solution was aged at -20 °C for 20-40 min with well-stirring to give a white to yellow suspension. The heterogeneous solution was again

cooled to -78 °C and quenched with the electrophile (neat if liquid, in a minimum amount of THF if solid). The mixture was kept at -78 °C for 2 hr and then allowed to come to ambient temperature overnight.

2.4.2.4 Work-up and Deprotection, Method A: Acid-catalyzed dehydroxymethylation

The solution from above was quenched with aqueous ammonium chloride at 0 °C, diluted with diethyl ether (100 mL) and carefully extracted (with shaking) with 2 N aqueous hydrochloric acid (4 x 30 mL). The aqueous extracts were combined and basified with aqueous ammonium hydroxide with efficient stirring at 0 °C. The aqueous layer was extracted with diethyl ether or ethyl acetate and the organic extract dried over sodium sulfate. The solvent was removed by rotary evaporation under reduced pressure to give the crude product, which was purified by recrystallization.

2.4.2.5 Work-up and Deprotection, Method B: Silica gel assisted dehydroxymethylation

After quenching with aqueous ammonium chloride and dilution with diethyl ether, the organic layer was separated, washed with brine (2 x 10 mL), and dried over sodium sulfate. The solvent was removed by rotary evaporation under reduced pressure to give an oily residue. The residue was allowed to pass through a silica gel column using appropriate solvents as eluents. The

product could be purified by recrystallization if solid. For liquid products, no further purification was employed.

Physical data of the products, yields, and methods of deprotection and purification are given in Table 2.1. The following compounds were prepared according to the procedure.

5(3)-(α-Phenyl-α-hydroxymethyl)pyrazole (**2.40a**). Microcrystalline solid (recrystallized from ethyl acetate), m.p. 113-114 °C, lit. [72BSF2764] m.p. 114 °C. ^{1}H-NMR (DMSO-d_6, TMS) δ 12.7 (bs, 1 H, NH), 7.25-7.50 (m, 6 H, H-3 or H-5 and phenyl protons), 6.08 (d, J = 2 Hz, H-4), 5.86 (s, 2 H, CH and OH); ^{13}C-NMR (DMSO-d_6) δ 144.2 (C-3), 135.2 (C-5), 127.8 (aromatic, C-ipso), 126.7 (aromatic, C-o), 126.1 (aromatic, C-m), 110.9 (aromatic, C-p), 101.9 (C-4), 68.4 (CHOH).

5(3)-[α-(p-Tolyl)-α-hydroxymethyl]pyrazole (**2.40b**). Microcrystalline solid (recrystallized from ethyl acetate), m.p. 95-97 °C. ^{1}H-NMR (DMSO-d_6, TMS) δ 12.7 (bs, 1 H, NH), 7.12-7.50 (m, 5 H, H-3 or H-5 and phenyl protons), 6.12 (d, J = 2 Hz, 1 H, H-4), 5.79 (m, 2 H, CH and OH), 2.25 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 141.6 (C-3), 135.7 (C-5), 130.2 (aromatic, C-ipso), 128.4 (aromatic, C-o), 126.1 (aromatic, C-m), 111.0 (aromatic, C-p), 101.9 (C-4), 68.8 (CHOH), 20.6 (CH_3).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.86. Found: C, 70.23; H, 6.43; N, 14.99.

5(3)-Phenylthiopyrazole (2.40c). Oil (from column chromatography, ethyl ether and 20% hexane). ^{1}H-NMR ($CDCl_3$, TMS) δ 12.5 (bs, 1 H, NH), 7.46 (d, J = 2 Hz, 1 H, H-3 or H-5), 7.08-7.28 (m, 5 H, phenyl protons), 6.38 (d, J = 2 Hz, 1 H, H-4); ^{13}C-NMR ($CDCl_3$) δ 140.8 (C-3), 136.4 (aromatic, C-ipso), 131.7 (C-5), 129.0 (aromatic, C-o), 128.4 (aromatic, C-m), 126.2 (aromatic, C-p), 110.5 (C-4).

Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.53; H, 4.59; N, 15.61.

5(3)-Benzylpyrazole (2.40d). Oil (from column chromatography, ethyl ether and 20% hexane), lit. [71JOC4033] b.p. 140-150 °C/0.05 mm Hg. ^{1}H-NMR ($CDCl_3$, TMS) δ 12.5 (bs, 1 H, NH), 3.95 (s, 2 H, CH_2), 7.28 (d, J = 2 Hz, 1 H, H-3 or H-5), 7.18 (s, 5 H, phenyl protons), 5.96 (d, J = 2 Hz, 1 H, H-4); ^{13}C-NMR ($CDCl_3$) δ 146.9 (C-3), 139.9 (aromatic, C-ipso), 133.3 (C-5), 128.5 (aromatic, C-o), 128.3 (aromatic, C-m), 126.1 (aromatic, C-p), 103.7 (C-4), 32.9 (CH_2).

5(3)-Benzylthiopyrazole (2.40e). Oil (from column chromatography, ethyl ether and 20% hexane, then ethyl acetate), lit. [56CA12029f] oil. ^{1}H-NMR ($CDCl_3$, TMS) δ

12.7 (bs, 1 H, NH), 7.46 (d, J = 2 Hz, 1 H, H-3 or H-5), 7.20 (s, 5 H, phenyl protons), 6.18 (d, J = 2 Hz, 1 H, H-4), 4.08 (s, 2 H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 146.3 (C-3), 137.5 (aromatic, C-ipso), 131.2 (C-5), 128.7 (aromatic, C-o), 128.4 (aromatic, C-m), 127.4 (aromatic, C-p), 109.2 (C-4), 39.1 (CH_2).

5(3)-(α,α-Diphenyl-α-hydroxymethyl)pyrazole (**2.40f**). Microcrystalline solid (recrystallized from ethyl acetate and pet. ether), m.p. 121-123 °C . ^{1}H-NMR ($CDCl_3$, TMS) δ 14.8 (1 H, NH), 7.21 (s, 10 H, phenyl protons), 7.01 (d, J = 2 Hz, H-3 or H-5), 5.80 (d, J = 2 Hz, 1 H, H-4), 5.20 (s, 1 H, OH); ^{13}C-NMR ($CDCl_3$) δ 153.9 (aromatic, C-ipso), 146.2 (C-3), 132.2 (C-5), 127.8 (aromatic, C-o), 127.4 (aromatic, C-m), 127.3 (aromatic, C-p), 105.2 (C-4), 78.1 (COH).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.46; H, 5.64; N, 11.26.

5(3)-Cyclohexanoylpyrazole (**2.40g**). Needles (recrystallized from ethyl acetate and pet. ether), m.p. 122-123 °C. ^{1}H-NMR (DMSO-d_6, TMS) δ 7.21 (d, J = 2 Hz, H-3 or H-5), 6.12 (d, J = 2 Hz, H-4), 4.73 (s, 1 H, OH), 1.95-1.21 (m, 10 H); ^{13}C-NMR (DMSO-d_6) δ 133.4 (C-3), 111.2 (C-5), 100.8 (C-4), 68.5 (COH), 38.1, 25.4, 21.8.

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.81; H, 8.53; N, 16.52.

5(3)-Phenylcarbamoylpyrazole (**2.40h**).

Microcrystalline solid (recrystallized from ethyl acetate and pet. ether), m.p. 125-127 °C. ^{1}H-NMR ($CDCl_3$, TMS) δ 10.09 (s, 1 H, NH), 7.28-8.01 (m, 6 H), 7.12 (d, J = 2 Hz, H-3 or H-5), 6.87 (d, J = 2 Hz, H-4); ^{13}C-NMR ($CDCl_3$) δ 160.5 (CONH), 146.7 (C-3), 138.8 (aromatic, C-ipso), 130.3 (C-5), 128.5 (aromatic, C-o), 123.4 (aromatic, C-m), 120.2 (aromatic, C-p), 105.6 (C-4).

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.24; H, 4.88; N, 22.65.

CHAPTER III

α-LITHIATION OF 1,2,4-TRIAZOLES

3.1 Introduction

3.1.1 The Important Industrial Applications of 3(5)-Substituted 1,2,4-Triazoles

3(5)-Substituted 1,2,4-triazoles are heterocyclic compounds with important industrial applications [84MI1]. Numerous publications, mainly patents, demonstrate their use in agriculture, pharmacy, dyestuffs, photography, and polymers [61CRV87, 84MI1]. The well-known 3-amino-1,2,4-triazole (Figure 3.1) has many commercial brand names (Amitrole, Amizol, ATA, Weedazol, etc.) and is the first 1,2,4-triazole to be manufactured on a large scale for use as a neutral herbicide and defoliant of cotton.

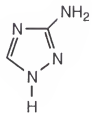


Figure 3.1 3-Amino-1,2,4-triazole

Many 3(5)-alkylthio-1,2,4-triazoles find useful applications in photography because they can react with silver compounds and form disulfides as potential free radicals [61CRV87, 84MI1]. 3(5)-Propargylthio-1,2,4-triazole (Figure 3.2) is known to effectively stabilize photographic emulsions [74GEP2304321].

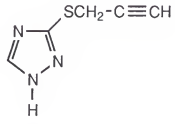


Figure 3.2 3-Propargylthio-1,2,4-triazole

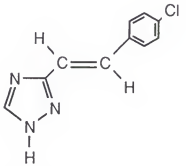


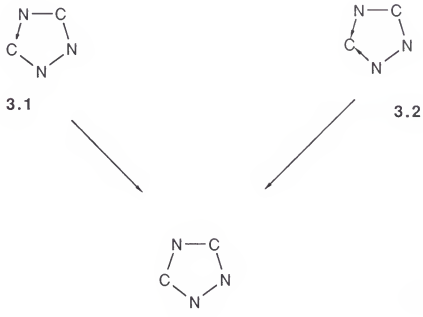
Figure 3.3 3-(4-Chlorostyryl)-1,2,4-triazole

It is well known that 3(5)-substituted 1,2,4-triazoles possess biological activities [61CRV87, 81HC251, 84MI1]. Many 3(5)-substituted 1,2,4-triazoles are widely used in agriculture as synergistic herbicides [61CRV87, 84MI1, 85GEP3332271]. Some 3(5)-substituted 1,2,4-triazoles display biological activity such as inhibition of cholinesterase [55MI1], interference with mitosis [51MI1] and reversible denaturation of serum proteins [52MI1]. 3-(4-Chlorostyryl)-1,2,4-triazole (Figure 3.3), when dimerized, shows biological activity against Candide albicans and Trichophyton mentagrophytes in mice [84EP122693].

3.1.2 General View of the Methods for the Preparation of 3(5)-Substituted 1,2,4-Triazoles

Numerous methods have been reported for the preparation of 3(5)-substituted 1,2,4-triazoles, most of which have disadvantages and limitations. Two types of approaches; synthesis from acyclic compounds and by ring transformation of other cyclic systems, are generally applied for the preparation of a triazole of this nature.

In the former approach, a cabon-nitrogen chain of one of the following types (**3.1**) and (**3.2**) undergoes cyclization to form the triazole ring (**3.3**) (Scheme 3.1)



Scheme 3.1

For almost half a century, ring closure from 3.1 has been preferred as the most efficient method of synthesis of 3(5)-substituted 1,2,4-triazoles. Generally, the acyclic compounds with this type of preformed skeleton are such that on the ring closure a triazole containing a thione or a hydroxy group is obtained, and this is then removed by oxidation [61CRV87]. The ring closure of such acyclic compounds usually employs thiosemicarbazide derivatives and the reaction is carried out in the presence of a base [49JCS1918, 55JA1538]. The removal of the thione group is effected by oxidation with nitric acid [1889CB576, 55JA1538, 68JIC(45)338]. However, this method has several limitations, the most severe of which is that the ring closure is ambiguous and mixtures with other heterocycles can be obtained. Other limitations include that the nature of the 3(5)-substituents introduced is limited by the transformation conditions of the acyclic precursor and the conditions for the removal of thione are incompatible with sensitive substituents.

The ring closure of 3.2 involves two acyclic precursors and again, ambiguity arises when there are several sites available to be linked. Thus the formation of a number of 3(5)-substituted 1,2,4-triazoles were accomplished by the condensation of amidrazones with ethyl

orthoformate and hydrazine, but yields were low to moderate since the self-condensation of amidrazones gave dihydrotetrazines and other heterocycles as by-products [62CB2546, 64CB528, 68CB2033, 71BCJ780].

Preparation of 3(5)-substituted 1,2,4-triazoles by ring transformation of other heterocyclic systems has been an active field in the chemistry of 1,2,4-triazole. In early studies, Grundmann and Kreutzberger [57JA2839] found that s-triazine was degraded to a number of 3(5)-substituted 1,2,4-triazoles by heating to 120 °C with appropriate reagents. Thus the reaction of s-triazine with semicarbazide, thiosemicarbazide, and aminoguanidine gave 3-hydroxy-, 3-mercapto-, and 3-amino-1,2,4-triazole in 19%, 64% and 48% yields, respectively. The low yields are due to ring transformation into other heterocycles and the decomposition of the acyclic intermediates.

Later, Potts and coworkers [69JOC3221, 70JOC3448] studied the ring transformations of fused-ring heterocycles including phthalazine and quinazoline, for the preparation of 3(5)-substituted 1,2,4-triazoles. However, the study was carried out mechanistically rather than synthetically. Under different reaction conditions, different ring systems were obtained and reactions were erratic. Again, the severe problem is that both ring cleavage and recyclization are ambiguous and the formation

of 1,2,4-triazole competes against that of other ring systems.

Ring transformation of pyrimidines to 3(5)-substituted 1,2,4-triazoles has been reported by van der Plas and coworkers [67TL4385, 70RT680]. Thus a number of 4,6-disubstituted pyrimidines were converted, on treatment with hydrazine in a sealed tube, into 3-methyl- and 3-ethyl-1,2,4-triazole in 55% and 90% yield, respectively. The reaction only took place at 210 °C; below 150 °C, pyrazole derivatives rather than triazoles were obtained. The same laboratory [74RT236] also reported the ring transformations of pyridazines to 3(5)-substituted 1,2,4-triazoles. Low yields were obtained and the reaction conditions were drastic.

More recently, Robev [82TL2903] reported the synthesis of various 3(5)-arylsubstituted 1,2,4-triazoles by ring transformation of dihydropyrimidines with hydrazine. Yields were moderate to good. However, the reaction requires the availability of the appropriate precursor and does not allow for versatility in the structural features of the products.

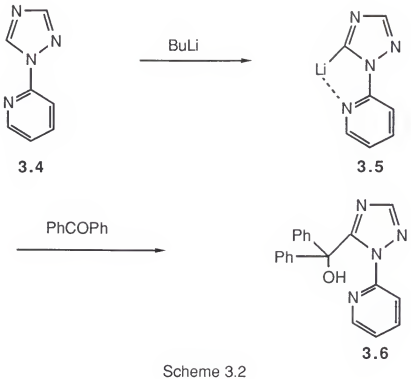
3.1.3 General View of the Lithiation of 1,2,4-Triazoles

1,2,4-Triazoles are probably among the most readily lithiated heterocycles because they contain three

electronegative nitrogen atoms which greatly increase the acidity of the α-hydrogen. Acidity measurements of various five-membered ring heterocycles in tetrahydrofuran using ^{13}C-NMR spectroscopy show that the pK_a value of 1-propyl-1,2,4-triazole is about 26.6, which is about 7 pK_a units more acidic than 1-methylimidazole (pK_a = 33.7), 10 pK_a units more acidic than 1-propylpyrazole (pK_a = 35.9) and 13 pK_a units more acidic than 1-methylpyrrole (pK_a = 39.5) [85CJC3505], respectively. Therefore, one can expect that 1,2,4-triazoles should be more amenable towards lithiation than the other heterocycles mentioned above. Surprisingly, in comparison with other azoles, the lithiation of 1,2,4-triazoles has received less attention, as seen by the fact that there are only a few literature reports on this subject.

The earliest literature data on the lithiation of 1,2,4-triazoles was reported by Fischer and coworkers [72AG(E)846] who found that the lithiation of 1-(2-pyridyl)-1,2,4-triazole (**3.4**) occurred smoothly at the C-5 position to give the corresponding 5-lithio species (**3.5**). This 5-lithio species reacted with benzophenone to give the corresponding alcohol (**3.6**) in good yield (70%) (Scheme 3.2).

Later, Behringer and Rament [75LA1264] reported that the lithiation of 1-benzyl-3-phenyl-1,2,4-triazole rapidly formed the 5-lithio species which, on treatment with various aromatic ketones, afforded the corresponding alcohols in high yields.

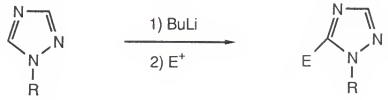


3.4 3.5 3.6

Scheme 3.2

Micetich et al. [85H1645] studied the sequential lithiation of 1-phenyl-1,2,4-triazoles. The initial lithiation proceeded smoothly at the C-5 position to give the 5-lithio-1-phenyl-1,2,4-triazole. This intermediate on reaction with the appropriate reagent was readily converted to the 5-substituted 1-phenyl-1,2,4-triazoles in good yields. Subsequent lithiation of various 5-substituted 1-phenyl-1,2,4-triazoles gave exclusively the lateral lithiated species which readily reacted with electrophiles, leading to the final products.

More recently, Anderson et al [86JHC1257] reported a detailed study on the lithiation of various 1-alkyl 1,2,4-triazoles (**3.7**), including 1-methyl-1,2,4-triazole (**3.7a**), 1-benzyl-1,2,4-triazole (**3.7b**) and 1-triphenylmethyl-1,2,4-triazole (**3.7c**). The authors found that 1-methyl-1,2,4-triazole (**3.7a**) and 1-benzyl-1,2,4-triazole (**3.7b**) lithiated smoothly and after quenching with various electrophiles, afforded the 5-substituted 1,2,4-triazoles (**3.8**) in good yields (Scheme 3.3).



3.7a R = CH_3
b R = $C_6H_5CH_2$
c R = $(C_6H_5)_3C$

3.8

Scheme 3.3

However, the lithiation study of 1-triphenylmethyl-1,2,4-triazole showed different results. When the lithiated species was quenched with deuteriomethanol it

resulted in a 92% yield of the 5-deuterated derivative. However, when the lithiated intermediate was quenched with diethylchlorophosphate none of the desired product was found. The large triphenylmethyl group evidently shields the lithiated 5-position, preventing the intermediate from reacting with the bulky chlorophosphate.

The regioselectivity of the lithiation of 1-alkyl 1,2,4-triazoles was also investigated and it was shown conclusively that the lithiation occurred exclusively at the C-5 position. The structure of the product was verified by an X-ray structural analysis [86JHC1257].

These results have shown that the lithiation of 1-substituted 1,2,4-triazoles represents a very useful route for the preparation of 1,5-disubstituted 1,2,4-triazoles.

3.1.3 Aim of the Work

The objective of the present work was to develop a new, general, and efficient route for the preparation of 3(5)-substituted 1,2,4-triazoles. The knowledge gained so far (Chapter II) and combined with literature precedents [72AG(E)846, 75LA1264, 74JOC940, 85H1645, 86JHC1257] suggested that the α-lithiation of N-protected 1,2,4-triazoles, followed by the addition of electrophiles and the removal of the N-protecting group, would constitute a straightforward and efficient route to the

3(5)-substituted 1,2,4-triazoles. As described above, the generation of α-carbanions via the lithiation of various N-alkyl and N-aryl 1,2,4-triazoles is a facile process and various substituents can be introduced via electrophilic addition. Thus the structural versatility available in the 1,5-disubstituted 1,2,4-triazoles prepared by this methodology is apparently more attractive than any other existing method for this class of compounds. However, little previous work has appeared on the use of N-protecting groups to enable C-lithiation in the 1,2,4-triazole series, followed by electrophilic attack and removal of the N-protecting group. The removal of N-alkyl and N-aryl groups is generally not facile and cannot be accomplished under mild reaction conditions. Thus the benzyl group appears to be an efficient N-protecting group for 1,2,4-triazoles, but the removal of a benzyl group usually requires rather strong conditions such as reductive cleavage by sodium in liquid ammonia [75LA1264, 74JOC940, 86JHC1257] or hydrogenolysis with Pt-C under pressure [86JHC1257] and in some cases both methods failed [86JHC1257]. Other N-alkyl or N-aryl groups such as methyl, phenyl and triphenylmethyl are even more difficult to remove and cannot be applied for synthetic purposes. Therefore, the use of an N-protecting group which can enable the α-lithiation effectively and can be removed readily under mild reaction conditions is crucial for the preparation of 3(5)-substituted 1,2,4-triazoles using the lithiation methodology.

The carbon dioxide (CO_2) methodology developed by Katritzky and coworkers is a powerful strategy for the α-lithiation of heterocycles containing an NH group. However, it failed with heterocycles containing two more nitrogen atoms (see Chapter II).

The hemiaminal method using formaldehyde as a protecting group has been successfully applied to the syntheses of 2-substituted benzimidazoles [89JOC2949] and 3(5)-substituted pyrazoles (Chapter II), but it failed with imidazoles and tetrazoles [89UP1]. The instability of the hemiaminals of these heterocycles is assumed to be the reason.

As it was described earlier (Chapter II), the directing and activating effects of aminal groups in α-lithiations were found to be prominent in several heterocycles including carbazoles, imidazole, benzimidazole and pyrazole [88JOC794, 88JOC5685]. In addition, the aminal groups were readily removed on gently warming with dilute hydrochloric acid whereas the other functionalities introduced remained intact under these conditions.

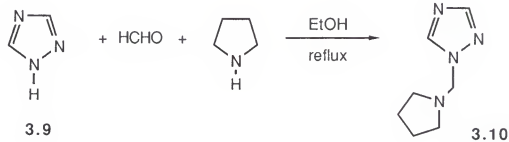
Based on these conclusive results, it was anticipated that the use of aminals as protecting and activating groups would be a useful tool for the α-lithiation of 1,2,4-triazoles. The introduction of an aminal group to heterocycles is a readily occurring reaction [73S703] and

hence, if the aminal group introduced can be removed under mild conditions, the strategy envisioned would provide a novel route for the preparation of 3(5)-substituted 1,2,4-triazoles with general scope.

3.2 Results and Discussion

3.2.1 Preparation of 1-(1-Pyrrolidinomethyl)1,2,4-triazole (3.10)

The aminal group selected for investigation was pyrrolidinomethyl since it has been shown previously to be effective as a protecting-activating group in the α-lithiation of heterocycles [88JOC794, 88JOC5685]. Both starting materials pyrrolidine and formaldehyde are commercially available and inexpensive. The preparation of 1-(1-pyrrolidinomethyl)-1,2,4-triazole (**3.10**) (87%) was readily accomplished under the modified Mannich reaction conditions by refluxing 1,2,4-triazole (**3.9**), formaldehyde and pyrrolidine in ethanol (Scheme 3.4).

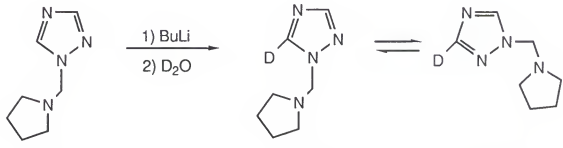


3.9 **3.10**

Scheme 3.4

3.2.2 Lithiation of 1-(1-Pyrrolidinomethyl)-1,2,4-triazole (3.10)

The initial lithiation of 1-(1-pyrrolidinomethyl)-1,2,4-triazole (**3.10**) was carried out by treatment with butyllithium in tetrahydrofuran at -78 °C, followed by quenching with deuterium oxide (D_2O) (Scheme 3.5).



3.10 **3.11aA** **3.11aB**

Scheme 3.5

However, the product isolated after workup (quenching with 2N hydrochloric acid) was shown by NMR analysis to be a mixture of two isomers: 3-deutero- (**3.11aB**) and 5-deutero-1-(1-pyrrolidinomethyl)-1,2,4-triazole (**3.11aA**).

The ^{1}H-NMR spectrum of compound **3.10** displayed two 1,2,4-triazole ring proton signals and the methylene group (CH_2) signal at 7.89 (H-3), 8.24 (H-5) and at 5.19 ppm (CH_2), respectively, with an integral ratio of 1:1:2. The

proton NMR spectrum of the deuterated compound (**3.11a**) also showed two different ring proton signals at 7.98 (H-3) and 8.25 ppm (H-5), and the CH_2 proton signal at 5.19 ppm. However, it was now in a ratio of 1:1:4, clearly indicating two isomers in a precisely 1:1 ratio. Further evidence was obtained from the ^{13}C-NMR spectrum of compound **3.11a** in which two ring carbon signals appeared as singlets at 150.7 (C-3) and 143.0 ppm (C-5) while two other ring carbon signals appeared as triplets with very low intensity at precisely the same positions as the two singlets. These two triplets were obviously due to the coupling effects of the incorporated deuteriums.

Similar results were observed when a number of electrophiles such as methyl iodide, benzaldehyde and p-tolualdehyde were employed. Thus when a methyl group was incorporated into the ring, the proton NMR spectrum of product (**3.11b**) also showed two different ring proton signals at 7.98 (H-3) and 8.20 ppm (H-5). However, unlike **3.11a**, two different CH_2 signals were observed at 5.15 ppm and 5.09 ppm, the integral ratios of which indicated that the amounts of the two isomers were unequal, with the 3-substituted isomer (**3.11bB**) slightly in excess (approximately 10:9 by integrals).

In the case of compound (**3.11c**), which was obtained by the reaction of the anion of triazole **3.10** with benzaldehyde, the proton NMR spectrum showed more

interesting patterns as seen in Figure 3.4. The two singlets at 8.03 ppm and 7.78 ppm were assigned to H-5 of the 3-substituted isomer (**3.11cB**) and H-3 of the 5-substituted isomer (**3.11cA**), respectively. Another two singlets at 6.10 ppm and 5.91 ppm, arise from the two CH groups of the isomers. However, the CH_2 signals from the two isomers now displayed different resonance patterns. The CH_2 group from the 3-substituted isomer appeared as a singlet at 5.05 ppm; whereas the CH_2 group of the 5-substituted isomer was split into two doublets, revealing a typical AB pattern at 4.55 ppm. The coupling constant of each doublet was about 12 Hz.

To explain this, two different isomers i.e. the 5-substituted triazole **3.11cA** and the 3-substituted isomer **3.11cB** are depicted in Figure 3.5. In compound **3.11cB**, since the chiral 3-substituent and the pyrrolidinomethyl group are far apart, the diasterotopic protons of the methylene group coincidently do not differ in the chemical shifts, thus giving rise to a singlet. However, the diasterotopic protons in compound **3.11cA** give rise to different signals for the following reasons: (i) the proximity between the chiral substituent and the pyrrolidinomethyl group; and (ii) the possible hydrogen bond formation between the hyroxyl and the pyrrolidino group, resulting in the formation of a seven-membered ring.

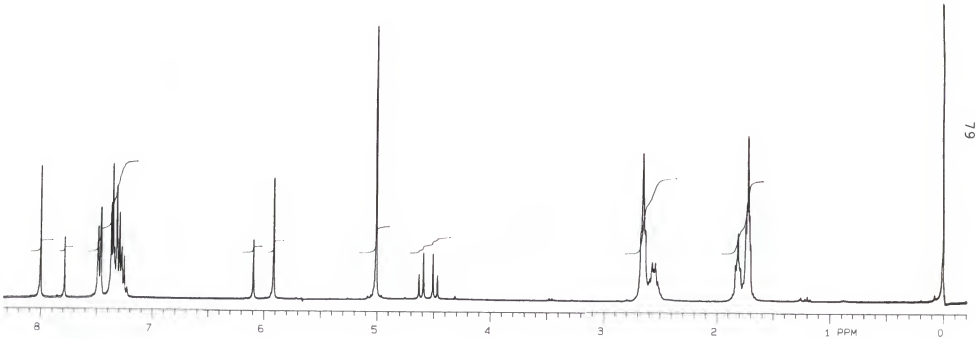


Figure 3.4 ^{1}H-NMR Spectrum of 3-(Phenylhydroxymethyl)-1-(1-Pyrrolidinomethyl)-1,2,4-triazole

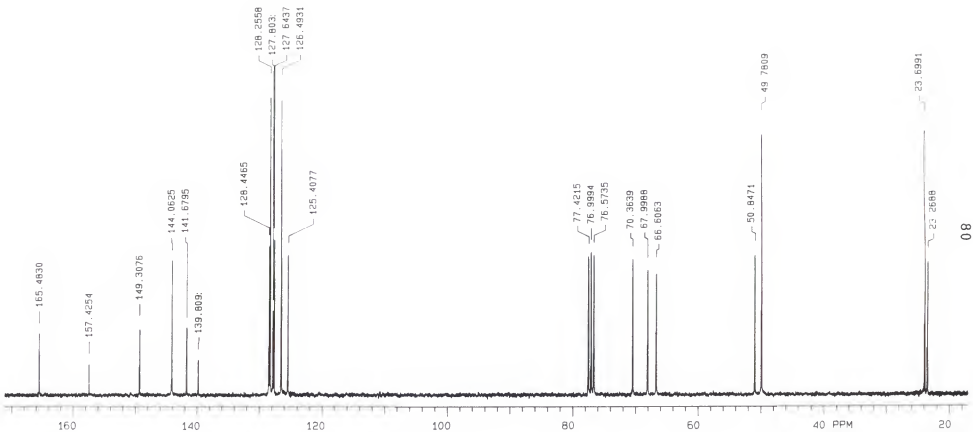
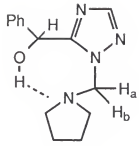
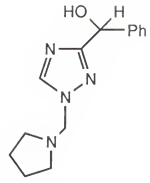


Figure 3.6 ^{13}C-NMR Spectrum of 3-(Phenylhydroxymethyl)-1-(1-Pyrrolidinomethyl)-1,2,4-triazole



3.11cA



3.11cB

Figure 3.5 3- and 5-Phenylhydroxymethyl-1-(Pyrrolidino-methyl)-1,2,4-triazole

The ^{13}C-NMR spectrum of compound **3.11c** is shown in Figure 3.6 and the assignment of signals was confirmed by the attached proton NMR test (APT). In Figure 3.6, the signals at 165.4 (C-3) and 144.1 ppm (C-5) are assigned to the 3-substituted isomer (**3.11cB**) while the signals at 157.4 (C-3) and 149.3 ppm (C-5) belong to the 5-substituted isomer (**3.11cA**).

The lithiation of compound **3.10** followed by addition of p-tolualdehyde also gave the product (**3.11d**) as a mixture of two isomers. The proton NMR spectrum of compound **3.11d** was similar to that of compound **3.11c** in which the CH_2 group of the 5-substituted isomer (**3.11dA**) displayed an AB pattern (J = 12 Hz) at 4.56 ppm. The integral ratio of the two isomers was approximately 7:4.

The ^{13}C-NMR spectrum of this compound showed the ring carbon signals of the 5-substituted isomer at 157.6 (C-5) and 149.3 ppm (C-3) and those of the 3-substituted isomer at 165.4 (C-3) and 144.0 ppm (C-5), respectively.

Further investigation with other electrophiles such as cyclohexanone and isocyanates gave even more interesting results. The lithiation of compound **3.10**, followed by quenching with cyclohexanone, afforded the product (**3.11e**) in 83% yield. However, the NMR spectra (^{1}H and ^{13}C) showed that in solution this compound exists predominantly as the 3-substituted isomer and the 5-substituted isomer only in negligible amount (ca. 6%). Similar results were observed with products (**3.11f**) and (**3.11g**) in which carbamoyl groups had been introduced.

The evidence for these structures was again based on the NMR spectral data. From the literature, the ^{13}C-NMR chemical shifts of solid 1H-1,2,4-triazole appear at 148.00 ppm (C-3) and 143.9 ppm (C-5) [83H1713]. This is in good agreement with the ^{13}C-NMR chemical shifts of 1-methyl-1,2,4-triazole in solution (150.4 ppm, C-3; and 143.5 ppm, C-5) [74JOC357]. Hence, in compound **3.10**, the downfield signal at 150.9 ppm was assigned to C-3 and the upfield signal at 143.0 ppm assigned to C-5. After lithiation, the ^{13}C-NMR spectra of the products isolated (**3.11e-3.11g**) all showed the C-3 signal to be very much weaker than the C-5 signal.

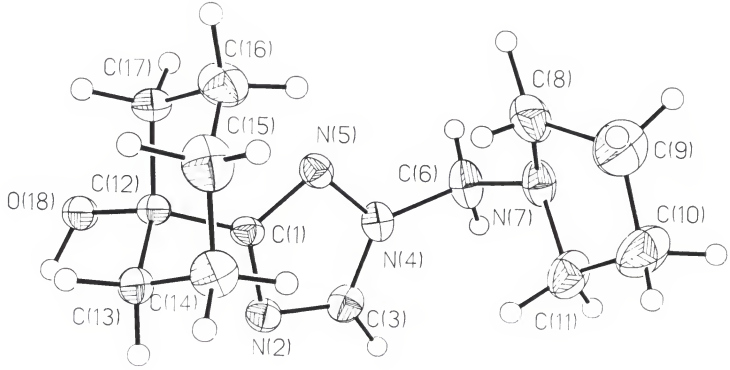


Figure 3.7 X-Ray Crystal Structure of 1-(1-Pyrrolidinomethyl)-3-cyclohexanolyl-1,2,4-triazole

Further proof was obtained from an X-ray structure analysis of **3.11e** which verified that the substituent was attached to C-3 (Figure 3.7). The crystal structure shows that in compound **3.11e**, the triazole ring occupies the axial position of the cyclohexyl ring, and the hydroxy group occupies the equatorial position. Although unusual, the axial substitution by the bulky pyrrolidinomethyltriazole group, is probably a consequence of favorable crystal packing.

These results were at first surprising since it was expected that the lithiation should give 5-substituted products, based on the literature. As was described earlier, the literature precedents in the lithiation of N-substituted 1,2,4-triazoles suggest that lithiation at the C-5 position is predominant and this regioselectivity has been further confirmed by the X-ray structural analysis of the product of 1-benzyl-1,2,4-triazole [86JHC1257]. In the present case, the aminal group should stabilize the adjacent carbanion by complexing the lithium atom and thus, the lithiation of compound **3.10** was certainly expected to occur at C-5 rather than C-3.

These unexpected results suggested that an isomerization process probably exists between 5-substituted 1,2,4-triazole (**3.11A**) and 3-substituted 1,2,4-triazole (**3.11B**) (Scheme 3.6): the lithiation surely results in the formation of **3.11A**, but subsequent isomerization favors the structurally more stable **3.11B** because of the lower steric hindrance.

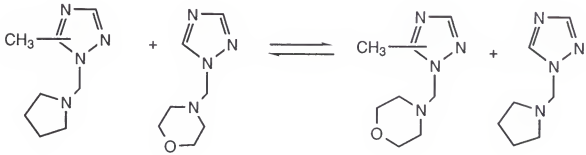
3.11A **3.11B**

a, E = D
b, E = CH_3
c, E = C_6H_5CHOH
d, E = p-$CH_3C_6H_4CHOH$
e, E = $(CH_2)_5COH$
f, E = t-BuNHCO
g, E = C_6H_5NHCO

Scheme 3.6

The isomerizations of various N-(1-aminoalkyl)-benzotriazoles have been intensively studied recently by Katritzky and coworkers [87JCS(P1)2673, 89H1121] and the mechanism was established as a dissociation-recombination process [89H1121]. Such facile "substituent" isomerization have been reported for a few other azoles with N-linked substituents, including R_3Si- (silylotropy) in benzimidazole [83H1713] or R_3Sn- (stannotropy) in pyrazoles [77JOM69]; however these processes have not been widely explored.

In order to confirm such isomerization in N-amino-alkyl-1,2,4-triazoles (3.11), a detailed NMR study was carried out; since the results described earlier could have been due to the formation of non interconverting isomers rather than to the formation of an equilibrium mixture.



3.11b **3.12** **3.13** **3.10**

Scheme 3.7

More conclusive information was gathered from a cross-over NMR experiment, in which simple mixing of equimolar amounts of compound (3.11b) and 1-(1-morpholino-methyl)-1,2,4-triazole (3.12) afforded spectral signals arising from the cross-over products (3.10) and (3.13), in addition to those from the starting materials (Scheme 3.7).

Specifically, the proton NMR spectrum of the mixture showed eight singlets in the aromatic region and six in the aliphatic NCH_2N region. If no cross-over products were formed, the expected number of signals would be four and three, respectively (Table 3.1). Partial overlapping of some of the peaks did not allow precise integration and assessment of isomeric distribution. Moreover, it was evident, that equilibrium was not attained instantaneously: the proton NMR spectrum examined after a few days, showed different ratios compared to the spectrum recorded immediately after mixing. Similarly, the ^{13}C-NMR spectrum displayed the anticipated number of peaks arising from **3.11** and **3.12** and cross-over products **3.13**, **3.10** (Table 3.1). This experiment confirmed that the isomerization is intermolecular, just as is the case with the corresponding benzotriazoles [87JCS(P1)2673]. However, although the isomerizations are spontaneous in both reactions, for the 1,2,4-triazoles they are somewhat slower.

In addition to the above evidence, variable temperature proton NMR experiments conclusively showed the occurrence of N-1 to N-2 interconversion: increase in the temperature resulted in peak broadening and eventual coalescence of the triazole ring signals. Thus the variable temperature proton NMR experiment of compound **3.11b** showed that the coalescence of the triazole ring signals started at 130 °C (in $CDBr_3$). The coalescence of the ring signals of compound 3.11c started at 115 °C (in $CDBr_3$).

Table 3.1 ^{1}H- and ^{13}C-NMR Chemical Shifts (δ) from the Cross-over Experiment in $CDCl_3$

Solution of	Triazole ring signals	NCH_2N
^{1}H-NMR		
3.11	8.07 7.78	5.03 5.01
3.12	8.15 7.95	5.00
3.11 + 3.12	8.18 8.17 8.04 8.02 7.97 7.95 7.79 7.78	5.14 5.03 5.01 5.00 4.90 4.84
^{13}C-NMR		
3.11	160.8 152.6 149.9 143.9	65.4 64.4
3.12	151.6 143.4	70.5
3.11 + 3.12	160.7 160.5 151.4 151.2 149.7 149.6 143.6 143.5 143.3 143.2	70.3 70.0 69.0 66.6 66.1 66.0

Several 3-substituted 1-(1-pyrrolidinomethyl)-1,2,4-triazoles (3.11) were isolated and characterized. Table 3.2 gives the isolated yields of various products along with its physical data for each of the electrophiles employed. Substituents introduced in this way into the 3-position of 1,2,4-triazole include an alkyl group from an alkyl halide (CH_3I); hydroxyalkyls from aldehydes and ketones; carbamoyls from isocyanates; and deuterium from deuterium oxide (D_2O). The yields are good to excellent and the procedures are simple. All new compounds were characterized by their ^1H (Table 3.3), ^{13}C-NMR (Table 3.4) spectra and by elemental analysis.

3.10

3.14a R = C_6H_5
b R = $C_6H_5CH_2$

Scheme 3.8

The lithiation of compound **3.10**, followed by addition of dialkyl disulfides, gave different results. When diphenyl disulfide was used as the electrophile, surprisingly, the deprotected 3(5)-phenylthio-1,2,4-triazole (**3.14a**) (57%) was the only product isolated under the normal workup conditions (aq. NH_4Cl quench) (Scheme 3.8). Similarly, compound (**3.14b**) (in which a benzylthio group was introduced) was isolated in 54% yield after workup under the same conditions. Nucleophilic cleavage of the aminal by the organosulfide anions formed in the reaction, forming stable thioaminals [54JA3969, 66MI11], presumably occurred. Such replacement was known in the case of benzotriazole adducts [89UP2]. However, the formation of deprotected products could be due to the hydrolysis of the aminal group during the workup even though it did not occur readily in the triazole case (see section 3.2.3). A conclusive result was obtained from a separate reaction in which equimolar amounts of **3.10** and sodium phenylthiolate were mixed and the ^1H and ^{13}C-NMR spectra of the mixture were recorded. New peaks at 4.65 ppm (CH_2, ^1H-NMR) and at 62.5 ppm (CH_2, ^{13}C-NMR) were observed, arising from the thioaminal [$PhSCH_2N(CH_2)_4$]. The chemical shifts were in good agreement with those of N-(phenylthiomethyl)-pyrrolidine, independently prepared from formaldehyde, pyrrolidine and sodium phenylthiolate.

Table 3.2 Preparation of Substituted 1-(1-Pyrrolidinomethyl)-1.2.4-triazoles (3.11)

Compd	Electrophile[a]	Substituent	Yield(%)[b]	M.p.(°C)
3.11a	D_2O	D	90	oil
3.11b	CH_3I	CH_3	95	oil
3.11c	C_6H_5CHO	C_6H_5CHOH	87	83-85
3.11d	$4\text{-}CH_3C_6H_4CHO$	$4\text{-}CH_3C_6H_4CHOH$	78	98-100
3.11e	cyclohexanone	$(CH_2)_5COH$	83	126-128
3.11f	$(CH_3)_3CNCO$	$(CH_3)_3CNHCO$	86	128-130
3.11g	C_6H_5NCO	C_6H_5NHCO	91	110-112

a. 1.0 to 1.1 eq. of electrophile was added at -78 °C.
b. Isolated yield. c. Uncorrected.

Table 3.3 ^{1}H-NMR Chemical Shifts (δ) for Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazoles (3.11) (ppm)

Compd	Triazole ring		NCH_2N	Pyrrolidino ring	
	H-3[a]	H-5[a]		α[b]	β[b]
3.11aA	7.98	-	5.19	2.76	1.78
3.11aB	-	8.25	5.19	2.76	1.78
3.11bA	7.98	-	5.09	2.78	1.78
3.11bB	-	8.20	5.15	2.78	1.78
3.11cA	7.78	-	4.55[c]	2.57	1.81
3.11cB	-	8.03	5.06	2.59	1.59
3.11dA	7.77	-	4.56[c]	2.58	1.81
3.11dB	-	8.42	5.05	2.59	1.59
3.11eB		8.09	5.12	2.73	d
3.11fB		8.31	5.21	2.72	1.75
3.11gB		8.81	5.27	2.66	1.65

a. Singlet. b. Multiplet, 4 H. c. dd, J = 12 Hz.
d. Immersed in the other protons.

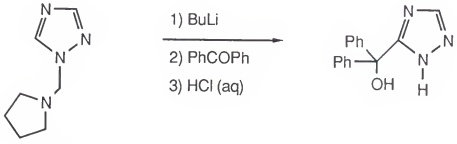
Table 3.4 ^{13}C-NMR Chemical Shifts (δ) for Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazoles (3.11) (ppm)

Compd	Triazole ring		NCH_2N	Pyrrolidino ring	
	C-3	C-5		α	β
3.11aA	150.8	143.0[a]	65.8	49.1	23.2
3.11aB	150.8[a]	143.0	65.8	49.1	23.2
3.11bA	148.9	159.3	64.1	48.9	22.4
3.11bB	151.4	143.0	64.9	48.6	22.3
3.11cA	149.3	157.4	66.6	50.9	23.2
3.11cB	165.4	145.1	69.1	49.0	23.4
3.11dA	149.3	157.6	67.9	50.9	23.3
3.11dB	165.6	144.0	66.6	49.8	23.7
3.11eB	169.6	143.5	66.4	49.8	23.7
3.11fB	157.2	144.1	67.0	49.5	23.5
3.11gB	156.7	146.0	66.2	49.0	23.5

a. Triplet.

3.2.3 Deprotection of 3-Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazoles

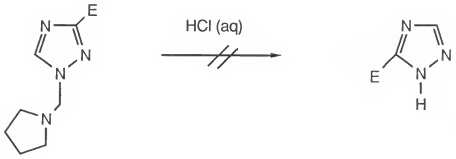
Hydrolysis of the protecting aminal group in 1-(dialkylaminomethyl)-benzimidazoles, -imidazoles and -pyrazoles is facile at room temperature using 2N hydrochloric acid during workup [88JOC5685, 88JOC794]. Surprisingly, hydrolysis of such aminal groups in 1-(1-pyrrolidinomethyl)-1,2,4-triazoles was more difficult. The only successful example was when benzophenone was used as the electrophile in which the aminal group was hydrolysed after stirring with 2N hydrochloric acid at room temperature for 2 hr, giving the deprotected triazole (**3.14c**) in 87% yield (Scheme 3.9).



3.10 **3.14c**

Scheme 3.9

However, attempted deprotection using hydrochloric acid (2 N) in refluxing ethanol for 12 hr, left compound **3.10** unchanged (Scheme 3.10). Compounds (**3.11b**) and (**3.11e**) were also unaffected under the same conditions, as indicated by the proton NMR spectra.



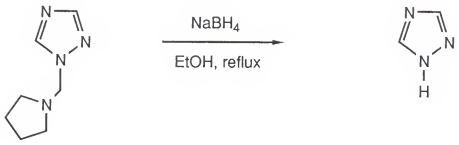
3.10 (E = H) and **3.11** **3.9** (E = H) and **3.14**

Scheme 3.10

Although on the basis of basicity and in comparison with benzimidazole, imidazole and pyrazole aminals, triazoles (**3.11**) should undergo facile cleavage under these reaction conditions, the results obtained were to the contrary and intriguing. Moreover, similar results were reported more recently in the case of 2-substituted N-(alkylaminomethyl)indoles in which the hydrolysis of the aminal group failed under various acidic conditions [89H849].

Since the acid-catalyzed hydrolysis of the aminal group was difficult for 1,2,4-triazoles, investigation of the deprotection under reductive conditions was attempted. As was described earlier (Chapter I), recent work by Katritzky et al has shown that various N-substituents of N-(dialkylaminomethyl)benzotriazoles are easily cleaved with sodium borohydride ($NaBH_4$) in ethanol or tetrahydrofuran to give free benzotriazole and the N-methyldialkylamines [87JCS(Pl)805, 88JCS(Pl)2339, 88TL1755]. If this method could be applied to the 1,2,4-triazole aminals, it would provide a powerful solution to the deprotection problem.

In the initial investigation, compound **3.10** was treated with an equimolar amount of sodium borohydride in refluxing ethanol for 2 hr. The reaction went smoothly and after workup, furnished 1,2,4-triazole **3.9** in almost quantitative yield (Scheme 3.11).

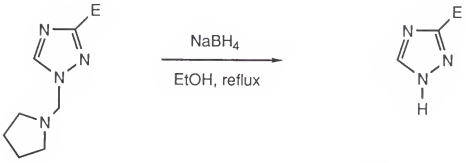


3.10 **3.9**

Scheme 3.11

This successful result led to its extension to 3-substituted 1-(1-pyrrolidinomethyl)-1,2,4-triazoles **3.11**. Indeed, deprotection was readily accomplished when compounds **3.11** were heated with sodium borohydride in ethanol for 2-3 hr (Scheme 3.12).

The results of the use of sodium borohydride as a deprotecting reagent for the N-protected 1,2,4-triazoles **3.11** are included in Table 3.5. As shown in the table, the yields of the deprotected products were generally high except in cases of compounds **3.14a-3.14b** which were obtained directly from the lithiation reaction. The substituents, including alkyl, hydroxyalkyl and carbamoyl, remained intact under these conditions.



3.11 **3.14**

Scheme 3.12

Table 3.5 Preparation of 3(5)-Substituted 1,2,4-triazoles (3.14)

Compound	3(5)-Substituent	Yield (%)[a]	M.p (°C)[b]
3.14a	C_6H_5S	57[c]	79-81
3.14b	$C_6H_5CH_2S$	54[c]	70-71
3.14c	$(C_6H_5)_2COH$	87[c]	226-227
3.14d	$(CH_2)_5COH$	98[d]	183-185
3.14e	CH_3	90[d]	92-94
3.14f	$(CH_3)_3CNHCO$	95[d]	175-177
3.14g	C_6H_5CHOH	91[d]	114-115
3.14h	$4\text{-}CH_3C_6H_4CHOH$	89[d]	121-122
3.14i	C_6H_5NHCO	98[d]	229-230

a. Isolated yield. b. Uncorrected. c. Isolated as deprotected product after workup in lithiation reaction. d. Deprotected product by using $NaBH_4$ in refluxing ethanol.

Table 3.6 Typical ^{1}H- and ^{13}C-NMR Chemical Shifts (δ) for 3(5)-Substituted 1,2,4-Triazoles (3.14) (ppm)

Compound	3(5)-Substituent	^{1}H-NMR		^{13}C-NMR	
		Triazole H-3 (H-5)	Triazole NH	C-3	C-5
3.14a	C_6H_5S	8.52 (s)[a]	-[c]	146.7	154.9
3.14b	$C_6H_5CH_2S$	8.10 (s)[b]	-[c]	146.7	156.2
3.14c	$(C_6H_5)_2COH$	7.98 (s)[b]	7.08 (bs)	148.4	162.2
3.14d	$(CH_2)_5COH$	7.98 (s)[b]	6.62 (bs)	148.8	164.1
3.14e	CH_3	8.05 (s)[b]	6.03 (bs)	148.1	154.4
3.14f	$(CH_3)_3CNHCO$	7.75 (s)[b]	-[c]	150.9	157.2
3.14g	C_6H_5CHOH	8.07 (s)[b]	-[c]	147.9	160.7
3.14h	$4\text{-}CH_3C_6H_4CHOH$	8.25 (s)[b]	6.88 (bs)	148.7	160.8
3.14i	C_6H_5NHCO	8.63 (s)[b]	-[c]	146.9	154.4

a. $CDCl_3$ as solvent. b. DMSO-d_6 as solvent. c. NH missing.

All the products were characterized by their ^{1}H- and ^{13}C-NMR spectra (Table 3.6 and 3.7), elemental analysis data and by comparison of the physical properties with literature data. Typically, the carbon chemical shifts of the triazole ring carbons are in the range of 146-150 ppm for C-3 and 155-165 ppm for C-5, which are in good accordance with literature data [86JHC1257]. The triazole ring proton signals generally appear as singlets in the range 8.0-8.5 ppm, easily distinguishable from the aromatic proton signals of the substituents.

3.3 Conclusions

The work described in this chapter, further demonstrates the unequivocal usefulness of the aminal protecting-activating lithiation methodology in the synthesis of α-substituted heterocycles, thereby providing a novel route to the 3(5)-substituted 1,2,4-triazoles. The isomerization of α-substituted N-(alkylaminomethyl)-1,2,4-triazoles is realized for the first time and reveals that the 3-substituted isomers are favored in the equilibrium and probably exist exclusively in the solid state (verified in the case of compound **3.11e**) because the steric hindrance in the 5-substituted isomers. The deprotection of the N-aminal group in triazoles **3.11** using acid-catalyzed hydrolysis fails in most cases. However,

the reductive elimination of the aminal group using sodium borohydride is effective and provides the deprotected products **3.14** in high yields, thereby accomplishing the ultimate aim of the present research. In view of the ease of introduction and of removal, the present method is superior to those previously available for the preparation of 3(5)-substituted 1,2,4-triazoles *via* lithiation reactions.

3.4 Experimental

3.4.1 General

The apparatus and general procedures applied in this Chapter are identical to those described in Chapter II with the addition that ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian VXR-300 (FT mode) spectrometer.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were pre-dried over 4Å molecular sieves and distilled under nitrogen from sodium/benzophenone ketyl immediately before use. Silica gel (230-400 mesh) was purchased from Merck.

Commercial 1,2,4-triazole (Aldrich), pyrrolidine (Aldrich), and butyllithium (Aldrich) were used without purification. Electrophiles were purified by standard methods before use.

3.4.2 Preparation of 1-(1-Pyrrolidinomethyl)-1,2,4-triazole (3.10)

Pyrrolidine (8.5 g, 0.12 mol) and formaldehyde (3.6 g, 10 mL, 0.12 mol; 37% aqueous solution) were mixed and dissolved in 50 mL of ethanol. The mixture was refluxed for 4 hr and the solvent was removed under reduced pressure. The oily residue was diluted with water and extracted with chloroform (3 x 25 mL). The combined extracts were dried with sodium sulfate and the solvent was concentrated to give an oil which was further distilled under reduced pressure to give a colorless oil (13.72 g, 82% yield). B.p. 98-100 °C/ 1.2 mmHg; ^{1}H-NMR ($CDCl_3$, TMS) δ 8.24 (s, 1 H, H-5), 7.98 (s, 1 H, H-3), 5.19 (s, 2 H, CH_2), 2.77 (m, 4 H), 1.78 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 150.9 (C-3), 143.0 (C-5), 65.9 (CH_2), 49.2, 23.3. MS (HR) for $C_7H_{11}N_4$ calcd: 151.0984 (M^+ - 1), found 151.0989.

3.4.3 Preparation of 3- and 5-Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazoles (3.11)

General Procedure. 1-(1-Pyrrolidinomethyl)-1,2,4-triazole (3.10) (1.52 g, 10 mmol) was dissolved in tetrahydrofuran (20 mL) and the solution was cooled to -78 °C with stirring under argon. Butyllithium (4.2 mL, 11 mmol, 2.5 M in hexane) was added slowly via a syringe over 10 min. A heavy precipitate formed immediately,

indicating the formation of the lithium salt. The mixture was stirred at -78 °C for 30 min and warmed to -25 °C and kept at that temperature for 30 min. The mixture was recooled to -78 °C and the electrophile (11 mmol) in THF (2 mL) was added dropwise via a syringe over 5 min. The reaction mixture was stirred at -78 °C for 3 hr and warmed to room temperature overnight. The reaction mixture was quenched with water (20 mL) and extracted with chloroform (4 x 25 mL). The combined extracts were dried with sodium sulfate and evaporated under reduced pressure to afford the crude product which was then purified as described for each particular compound.

3- and 5-Deutero-1-(1-pyrrolidinomethyl)-1,2,4-triazole (**3.11a**). A clean, pale yellow oil (90%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 2:1, v/v). Isomer A: ^{1}H-NMR ($CDCl_3$, TMS) δ 7.98 (s, 1 H, H-3), 5.19 (s, 2 H, NCH_2N), 2.76 (m, 4 H), 1.78 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 150.8 (triplet, C-5), 143.0 (C-3), 65.8 (NCH_2N), 49.1, 23.2. Isomer B: ^{1}H-NMR ($CDCl_3$, TMS) δ 8.25 (s, 1 H, H-5), 5.19 (s, 2 H, NCH_2N), 2.76 (m, 4 H), 1.78 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 150.8 (C-5), 143.0 (triplet, C-3), 65.8 (NCH_2N), 49.1, 23.2. Mass spectrum, m/z (relative intensity): 152 (1.8, M^+ - 1), 96 (0.28, M^+ - 57), 84 (100, M^+ - 69), 83 (80), 55

(21), 42 (31), 41 (11). MS (HR) for $C_7H_{10}DN_4$ calcd: 152.1046; found: 152.1056.

3- and 5-Methyl-1-(1-pyrrolidinomethyl)-1,2,4-triazole (3.11b). A clean, pale yellow oil (95%) was obtained after column chromatography (silica gel, from diethyl ether and hexane, 80:20, v/v). Isomer A: ^{1}H-NMR ($CDCl_3$, TMS) δ 7.98 (s, 1 H, H-3), 5.09 (s, 2 H, NCH_2N), 2.78 (m, 4 H), 2.58 (s, 3 H, CH_3), 1.78 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 159.3 (C-5), 148.9 (C-3), 64.1 (NCH_2N), 48.9 22.4, 12.6 (CH_3). Isomer B: ^{1}H-NMR ($CDCl_3$, TMS) δ 8.20 (s, 1 H, H-5), 5.15 (s, 2 H, NCH_2N), 2.78 (m, 4 H), 2.39 (s, 3 H, CH_3), 1.78 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 151.4 (C-3), 143.0 (C-5), 64.9 (NCH_2N), 48.6, 22.3, 10.7 (CH_3). MS (HR) for $C_8H_{14}N_4$ calcd: 165.1140; found: 165.1142.

[1-(1-Pyrrolidinomethyl)-1,2,4-triazol-3- and -5-yl] phenylcarbinol (3.11c). Needles (87%) (recrystallized from ethyl acetate and diethyl ether, 70:30, v/v), m.p. 83-85 °C. Isomer A: ^{1}H-NMR (DMSO-d_6, TMS) δ 7.78 (s, 1 H, H-3), 7.26-7.48 (m, 5 H, aromatic protons), 6.10 (s, 1 H, CH), 4.55 (dd, J = 12, 12 Hz, 2 H, NCH_2N), 2.57 (m, 4 H), 1.81 (m, 4 H); ^{13}C-NMR (DMSO-d_6) δ 157.4 (C-5), 149.3 (C-3)., 139.8 (C-ipso, phenyl), 127.8 (C-o, phenyl), 127.6 (C-m, phenyl), 125.4 (C-p, phenyl), 68.0 (CHOH), 66.6

(NCH_2N), 50.9, 23.3. Isomer B: ^{1}H-NMR (DMSO-d_6, TMS) δ 8.03 (s, 1 H, H-5), 7.26-7.48 (m, 5-H, aromatic protons), 5.91 (s, 1 H, CH), 5.06 (s, 2 H, NCH_2N), 2.59 (m, 4 H), 1.59 (m, 4 H); ^{13}C-NMR (DMSO-d_6) δ 165.4 (C-3), 145.1 (C-5), 143.1 (C-ipso, phenyl), 127.8 (C-m, phenyl), 126.9 (C-o, phenyl), 126.5 (C-p, phenyl), 69.1 (NCH_2N), 68.0 (CHOH), 49.0, 23.4.

Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.35; H, 6.91; N, 21.94.

[1-(1-Pyrrolidinomethyl)-1,2,4-triazol-3- and -5-yl]-p-tolylcarbinol (3.11d). Needles (78%) (recrystallized from chloroform and hexane, 90:10, v/v), m.p. 98-100 °C. Isomer A: ^{1}H-NMR ($CDCl_3$, TMS) δ 7.77 (s, H-3), 7.23 (d, J = 8 Hz, 2 H), 7.17 (d, J = 8 Hz, 2 H), 6.05 (s, 1 H, CH), 4.56 (dd, J = 12, 12 Hz, 2 H, NCH_2N), 2.58 (m, 4 H), 2.34 (s, 3 H, CH_3), 1.81 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 157.6 (C-5), 149.3 (C-3), 137.5 (C-ipso, phenyl), 136.8 (C-o, phenyl), 129.1 (C-m, phenyl), 125.3 (C-p, phenyl), 69.1 (NCH_2N), 68.0 (CH), 49.0, 23.4. Isomer B: ^{1}H-NMR ($CDCl_3$, TMS) δ 8.42 (s, H-5), 7.36 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8 Hz, 2 H), 5.88 (s, 1 H, CH), 5.05 (s, 2 H, NCH_2N), 2.59 (m, 4 H), 2.31 (s, 3 H, CH_3), 1.59 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 165.6 (C-3), 144.0 (C-5), 138.8 (C-ipso, phenyl), 137.3 (C-o, phenyl), 128.7 (C-m,

phenyl), 126.6 (C-p, phenyl), 70.3 (CH), 66.6 (NCH_2N), 49.8, 23.7, 21.3 (CH_3).

Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.16; H, 7.40; N, 20.57. Found: C, 65.96; H, 7.40; N, 20.78.

1-[(1-Pyrrolidinomethyl)-1,2,4-triazol-3-yl]-cyclohexanol (**3.11e**). Needles (83%) (recrystallized from benzene and petroleum ether, 90:10, v/v), m.p. 125-128 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 8.09 (s, 1 H, H-5), 5.12 (s, 2 H, NCH_2N), 3.98 (bs, 1 H, OH), 2.61-2.84 (m, 4 H), 1.21-2.21 (m, 14 H); ^{13}C-NMR ($CDCl_3$) δ 169.6 (C-3), 143.5 (C-5), 70.3 (COH), 66.4 (NCH_2N), 49.8, 37.2, 25.3, 23.7, 21.8.

Anal. Calcd for $C_{13}H_{22}N_4$: C, 62.37; H, 8.86; N, 22.38. Found: C, 62.73; H, 8.90; N, 22.20.

3-t-Butylcarbamoyl-1-(1-pyrrolidinomethyl)-1,2,4-triazole (**3.11f**). Needles (86%) (recrystallized from 85% ethanol), m.p. 128-130 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 8.31 (s, 1 H, H-5), 7.08 (bs, 1 H, NH), 5.21 (s, 2 H, NCH_2N), 2.72 (m, 4 H), 1.75 (m, 4 H), 1.48 (s, 9 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 158.2 (HNCO), 157.2 (C-3), 144.1 (C-5), 67.0 (NCH_2N), 51.2 [$(CH_3)_3C$], 49.5, 28.4 (CH_3), 23.5.

Anal. Calcd for $C_{12}H_{21}N_5O$: C, 57.35; H, 8.42; N, 27.86. Found: C, 62.73; H, 8.90; N, 22.20.

3-Phenylcarbamoyl-1-(1-pyrrolidinomethyl)-1,2,4-triazole (3.11g). Needles (91%) (recrystallized from 85% ethanol), m.p. 110-112 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 10.39 (bs, 1 H, NH), 8.81 (s, 1 H, H-5), 7.84 (m, 2 H, phenyl), 7.12-7.39 (m, 3 H, phenyl), 5.27 (s, 2 H, NCH_2N), 2.66 (m, 4 H), 1.65 (m, 4 H); ^{13}C-NMR (DMSO-d_6) δ 157.6 (CONH), 156.7 (C-3), 146.0 (C-5), 138.3 (C-ipso, phenyl), 128.7 (C-o, phenyl), 124.0 (C-m, phenyl), 120.5 (C-p, phenyl), 66.2 (NCH_2N), 49.0, 23.5.

Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 62.34; H, 5.96; N, 25.99.

3.4.4 Deprotection of 3- and 5-Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazoles with Sodium Borohydride

General Procedure. To a three-necked, 100 mL round bottom flask with a condenser, 20 mL of absolute ethanol and sodium borohydride (0.2 g, 5 mmol) were added. To this solution, the protected 1,2,4-triazole (5 mmol) in 10 mL of ethanol was added dropwise (added portionwise in the case of the protected 1,2,4-triazole which is insoluble in ethanol) and the mixture was refluxed for 2-3 hr. Following which, the ethanol solution was evaporated under reduced pressure to give a solid residue. The residue was dissolved in water and the water solution was continuously extracted with ethyl acetate in a liquid-liquid extraction

apparatus. The extracts were dried with sodium sulfate and evaporated to give the crude product which was purified as described for each particular compound. For compounds (**3.14a**), (**3.14b**) and (**3.14c**), the deprotected product was isolated after workup in the lithiation reaction and the procedure for each individual compound is specified below.

3(5)-Phenylthio-1,2,4-triazole (**3.14a**).
1-(1-Pyrrolidinomethyl)-1,2,4-triazole (**3.10**) (1.52 g, 10 mmol) was dissolved in dried THF (25 mL) and butyllithium (4.2 mL, 11 mmol, 2.5 M in hexane) was added dropwise via a syringe at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 min and warmed to -5 °C within 40 min. The solution was recooled to -78 °C and diphenyl disulfide (2.24 g, 10 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred at -78 °C for 3 hr and warmed to room temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride (NH_4Cl) and the aqueous solution was continuously extracted with ethyl acetate. The extracts were dried with sodium sulfate and evaporated to give an oily residue which was gradually solidified upon stand in air for one day. The solid residue was treated with ethyl ether and filtered. The pure compound (57%) was obtained by recrystallization from benzene and hexane (50:50). Needles, m.p. 79-81 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 8.62 (s,

1 H, H-3 or H-5), 7.19-7.58 (m, 5 H, phenyl); ^{13}C-NMR (DMSO-d_6) δ 154.9 (C-5), 146.7 (C-3), 132.7 (C-ipso, phenyl), 130.1 (C-m, phenyl), 129.3 (C-o, phenyl), 127.3 (C-p, phenyl).

Anal. Calcd for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71. Found: C, 54.21; H, 4.03; N, 23.80.

3(5)-Benzylthio-1,2,4-triazole (**3.14b**).
1-(1-Pyrrolidinomethyl)-1,2,4-triazole (**3.10**) (2.28 g, 15 mmol) was dissolved in THF (30 mL) and butyllithium (6.2 mL, 15.5 mmol, 2.5 M in hexane) was added dropwise at -78 °C under argon. The reaction mixture was stirred at -78 °C for 30 min and warmed to -5 °C within 40 min. The solution was recooled to -78 °C and dibenzyl disulfide (3.82 g, 15.5 mmol) in THF (5 mL) was added slowly at -78 °C. The reaction mixture was stirred at -78 °C for 3 hr and warmed to room temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride (NH_4Cl) and extracted with ethyl acetate (4 x 25 mL). The extracts were dried with sodium sulfate and evaporated under reduced pressure to give an oily residue which was gradually solidified upon stand in air for one day. The solid was treated with diethyl ether and hexane and filtrated to give needles (1.55 g, 54%). No further purification was needed. M.p. 70-71 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 8.10 (s, 1 H, H-3 or H-5), 7.15-7.38 (m,

5 H, phenyl), 4.13 (s, 2 H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 156.2 (C-5), 146.7 (C-3), 136.5 (C-ipso, phenyl), 128.6 (C-m, phenyl), 128.4 (C-o, phenyl), 127.4 (C-p, phenyl), 37.2 (CH_2).

Anal. Calcd for $C_9H_9N_3S$: C, 56.52; H, 4.74; N, 21.97. Found: C, 56.64; H, 4.70; N, 21.57.

1,2,4-Triazol-3- and -5-yldiphenylcarbinol (**3.14c**). 1-(1-Pyrrolidinomethyl)-1,2,4-triazole (**3.10**) (0.76 g, 5 mmol) was dissolved in diethyl ether (25 mL) and butyllithium (2.1 mL, 5.1 mmol, 2.5 M in hexane) was added dropwise at -78 °C under argon. A white precipitate was immediately formed. The reaction mixture was stirred at -78 °C for 1 hr and warmed to -25 °C and kept at this temperature for 30 min. The solution was recooled to -78 °C and benzophenone (0.98 g, 5.1 mmol) in diethyl ether (2 mL) was added slowly. Upon addition, a blue color immediately formed. The reaction mixture was stirred at -78 °C for 3 hr and warmed to room temperature overnight. The reaction mixture was quenched with hydrochloric acid (2 N, 20 mL) and stirred at room temperature for 2 hr. The solution was neutralized with solid sodium bicarbonate and a heavy precipitate was formed. The precipitate was filtered to give the crude product which was

recrystallized from 95% ethanol to give 1.02 g (87%) of pure compound. Needles, m.p. 226-227 °C; lit [86JHC1257] m.p. 226-227 °C; ^{1}H-NMR (DMSO-d_6, TMS), 7.98 (s, 1 H, H-3 or H-5), 7.18-7.58 (m, 10 H, phenyl), 7.08 (bs, 1 H, NH), 2.58 (bs, 1 H, OH); ^{13}C-NMR (DMSO-d_6) δ 162.2 (C-5), 148.4 (C-3), 145.8 (C-ipso, phenyl), 127.6 (C-m, phenyl), 126.8 (C-o, phenyl), 76.8 (COH).

1-(1,2,4-Triazol-5- or -3-yl)cyclohexanol (**3.14d**). Plates (98%) (recrystallized from 85% ethanol), m.p. 183-185 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 7.98 (s, 1 H, H-3 or H-5), 6.62 (bs, 1 H, NH), 5.32 (bs, 1 H, OH), 1.18-2.12 (m, 10 H); ^{13}C-NMR (DMSO-d_6), δ 164.1 (C-5), 148.8 (C-3), 68.8 (COH), 36.8, 25.1, 21.4.

Anal. Calcd for $C_8H_{13}NO$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.32; H, 8.00; N, 25.41.

3(5)-Methyl-1,2,4-triazole (**3.14e**). Granules (90%) (recrystallized from benzene), m.p. 92-94 °C; lit. [53JOC218] m.p. 94-95 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 8.05 (s, 1 H, H-3 or H-5), 6.03 (bs, 1 H, NH), 2.35 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 154.4 (C-5), 148.1 (C-3), 12.1 (CH_3).

3(5)-t-Butylcarbamoyl-1,24-triazole (3.14f). Granules (95%) (recrystallized from benzene and chloroform, 80:20, v/v), m.p. 175-177 °C; ^{1}H-NMR (DMSO-d_6, TMS), δ 7.75 (s, 1 H, H-3 or H-5), 7.30 (bs, 1 H, NH), 1.39 (s, 9 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 162.6 (NHCO), 157.2 (C-5), 150.9 (C-3), 49.9 [$(CH_3)_3\underline{C}$], 28.8 (CH_3).

Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.67; H, 7.16; N, 33.60.

3(5)-(α,α-Phenylhydroxylmethyl)-1,2,4-triazole (3.14g). Microcrystals (91%) (recrystallized from 75% ethanol), m.p. 114-115 °C; lit. [68JCS(C)824] m.p. 116-117 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 8.07 (s, 1 H, H-3 or H-5), 7.25-7.45 (m, 5 H, phenyl), 6.23 (bs, 1 H, OH), 5.86 (s, 1 H, CH); ^{13}C-NMR (DMSO-d_6) δ 160.7 (C-5), 147.9 (C-3), 142.5 (C-ipso, phenyl), 128.1 (C-m, phenyl), 127.4 (C-o, phenyl), 126.6 (C-p, phenyl), 68.7 (CHOH).

3(5)-(α,α-p-Tolylhydroxylmethyl)-1,2,4-triazole (3.14h). Granules (89%) (recrystallized from ethyl acetate and ethyl ether, 80:20, v/v), m.p. 121-122 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 8.24 (s, 1 H, H-3 or H-5), 7.57 (d, J = 8 Hz, 2 H, phenyl), 7.40 (d, J = 8 Hz, 2 H, phenyl), 6.88 (bs, 1 H, NH), 6.45 (bs, 1 H, OH), 6.07 (s, 1 H, CH), 2.54 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 160.8 (C-5), 148.7

(C-3), 139.5 (C-ipso, phenyl), 136.5 (C-m, phenyl), 128.6 (C-o, phenyl), 126.5 (C-p, phenyl), 68.5 (CHOH), 20.7 (CH_3).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.45; H, 5.86; N, 22.21. Found: C, 63.15; H, 5.81; N, 22.46.

3(5)-Phenylcarbamoyl-1,2,4-triazole (3.14i). Needles (98%) (recrystallized from 85% ethanol), m.p. 229-230 °C; lit. [79JOC99] m.p. 230-231.5 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 10.52 (s, 1 H, amide NH), 8.63 (s, 1 H, H-3 or H-5), 7.86 (m, 2 H, phenyl), 7.13-7.38 (m, 3 H, phenyl); ^{13}C-NMR (DMSO-d_6) δ 157.0 (NHCO), 154.4 (C-5), 146.9 (C-3), 138.3 (C-ipso, phenyl), 128.7 (C-m, phenyl), 124.1 (C-o, phenyl), 120.5 (C-p, phenyl).

3.4.5 X-Ray Crystal Structure Analysis of 1-(1-Pyrrolidinomethyl)-1,2,4-triazol-3-yl-cyclohexanol (3.11e)

The crystal structure of (3.11e) was determined by X-ray diffraction. Colorless crystals of (3.11e) suitable for diffraction studies were grown by slow evaporation of a benzene solution. The crystals are monoclinic, space group $P2_1/c$, with four molecules per unit cell. The dimensions are a = 12.754(2), b = 12.593(4), c =8.898(3) Å and β = 103.50(2)°. The cell volume is 1395.6(6) Å^3 and for a molecular weight of 250.364 amu, the calculated

density is 1.196 g/cm^3. A crystal 0.21 x 0.22 x 0.22 mm was used to measure 2834 reflection of which 1525 with Fobs > 3 σ(Fobs) were used in the analysis. The final R was 0.044 and R_w was 0.043 with a GOF of 1.29. The weighting scheme was $w = 1/\sigma(Fobs)^2$ and an empirical extinction correction parameter of 0.00056 was determined. All calculations were carried out using the SHELXTL system on a Model-30 Eclipse. All measurements were made using a Nicolet R3m diffractometer with graphite monochromatized MoK_α radiation. Final positional parameters, bond distances and angles have been deposited in the Cambridge X-ray data center.

Semiemprical calculations were carried out using the MOPAC program, version 3.0 on Micro VAX II by Mrs. Zhe-Ying Zhang of this department.

CHAPTER IV

DIRECTED LITHIATION OF BENZENESULFINAMIDES

4.1 Introduction

The direct replacement of an aromatic hydrogen atom by a metal is known as aromatic metallation [79OR(26)1]. In particular, when an organolithium compound is used, this is denoted "aromatic lithiation". The use of organolithium compounds as metallation agents dates back to 1928, when it was discovered that ethyllithium reacts with fluorene to produce 9-fluorenelithium, and similarly with several analogous hydrocarbons [28LA192]. However, aromatic metallation, where replacement of a hydrogen atom by lithium occurs at an sp^2-hybridized aromatic carbon atom to form a covalent lithium-carbon bond, was discovered independently by Wittig [38CB1903] and by Gilman [54OR258] during the 30's. From then on, enormous efforts have been devoted by organic chemists to the development of the area. Efforts have been concentrated on the discovery of new functional groups which promote metallations, the elaboration of novel heterocyclic and olefinic substrates as metallatable species, the fashioning of new types of lithiating agents, and the

establishment of the mechanism of metallation. Accordingly, the aromatic metallation reaction has evolved as an important strategy in aromatic and heterocyclic synthesis. Several reviews by leading chemists have appeared on the subject [54OR258, 74MI1, 79OR(26)1, 82ACR306, 83S597].

4.1.1 General Aspects of Directed Lithiation Reactions

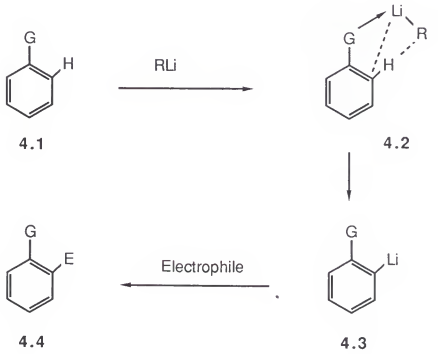
Although the term "aromatic lithiation" denotes the replacement of a hydrogen atom attached to an aromatic ring by lithium, benzene, the simplest aromatic compound, is lithiated only very slowly by butyllithium in solvents such as hexane, diethyl ether, or tetrahydrofuran (THF) and yields are negligible [74MI1]. However, in the presence of tetramethylethylenediamine (TMEDA), benzene can be lithiated in THF rapidly in good yield by the same reagent [65MI1]. TMEDA enhances the rate of lithiation by depolymerizing the normally hexameric butyllithium to the kinetically more reactive monomer by coordination of the nitrogen atoms of the bidentate ligand with the lithium atom.

A similar phenomenon, which has been known for many years, is that the lithiation rate can be dramatically enhanced when a heteroatom is attached to the aromatic ring. For example, simple benzene derivatives such as

phenol, phenol ethers, aniline, dimethylaniline, fluorobenzene, which have a substituent carrying an electron-donor heteroatom (atom with an unshared electron pair), can be lithiated even in the absence of TMEDA [54OR258, 74MI1, 79OR(26)1]. The mechanism of these heteroatom-facilitated lithiations has been assumed to involve initial coordination of the electron-deficient lithiating agent with the nonbonding electrons in the heteroatom (with attendant depolymerization). This coordination is then followed by a protophilic attack of the carbanionic portion of the lithiating agent on the adjacent hydrogen atom, leading to the lithiated product [46JA1658] (Scheme 4.1). Other mechanistic explanations such as the "coordination only" mechanism and the "acid-base" mechanism are only complements to the above and can be applied in the limiting case where one effect contributes far greater than the other to the observed phenomena [79(OR(26)1].

Another remarkable feature which is consistent with the rate enhancement is that, in almost every case, lithiation occurs exclusively ortho to the heteroatom substituent, regardless of whether the substituent is electron-withdrawing or electron-donating. This can be also well explained by the above mechanism since most heteroatom substituents contain lone pairs of electrons

which are available for coordination to the organolithium reagents. In the transition state, the coordinated organolithium compound would be held close to the ortho-position rather than the meta-/or para-position (Scheme 4.1). As a result, the subsequent protophilic attack would occur at the ortho position. This, indeed, is found to be the case and a variety of substituents, which are known to bring about ortho-lithiations, contain such a heteroatom. Furthermore and perhaps the most interesting feature to be noted here is that the lithiation-directing substituents include both those which are ortho/para-directing and meta-directing in normal acid catalyzed electrophilic substitution reactions. In lithiation, all these groups are only ortho-directing.



Scheme 4.1

Since directed lithiation is highly regioselective and the subsequent electrophilic substitutions are oriented, directed lithiation provides a general method for the introduction of electrophiles to positions normally not sufficiently reactive to give substitution in any meaningful yield by the classical acid catalyzed electrophilic substitution reactions. Through directed lithiation, syntheses of many heterocyclic compounds and natural products, which are not available by other methods, have now been successfully achieved [82ACR306, 83S597].

Directed ortho metallations with metals other than lithium have also been studied extensively and used for synthetic purposes [70ACR139, 77AG(E)73, 70ACR338, 76MI1, 77MI1]. However, the economy and high reactivity of organolithium compounds as well as their lack of toxicity, clearly make heteroatom-directed lithiation a more generally acceptable and practical method. It has been well recognized that heteroatom directed lithiation is now one of the most thriving areas in organic chemistry.

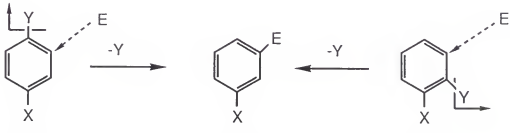
4.1.2 Aim of the Work

The introduction of a substituent at the meta-position to an ortho/para directing group is a classical problem of organic chemistry [65MI2]. A traditional solution is nitration at the ortho/para position to the

existing group, followed by reduction, substitution ortho/para to the now dominating amino group, and elimination of the amino group [44OR262, 61QR418]. Other methods include: (i) the temporary introduction of sulfonic acid groups as directing and/or blocking substituents, followed by desulfonation [65MI3]; (ii) the reversible modification of the ortho/para-directing substituent into a meta-directing group; the amino group is an example since, the free base form is highly ortho/para-directing, whereas the conjugated acid is deactivated and therefore meta-directing [71S455]; (iii) use of arenechromium tricarbonyl complexes as directing and/or blocking groups followed by addition of a nucleophile and removal of chromium tricarbonyl by oxidation [77JA1675, 79JA3535, 81T3957].

All these methods suffer from disadvantages such as: (i) the number of substituents introduced is limited by the nature of the directing group [44OR262, 61QR418, 65MI3, 71S455, 77JA1675, 79JA3535]; (ii) the substitution reactions are frequently not regiospecific and a number of side reactions compete simultaneously [71S455, 77JA1675, 79JA3535] and (iii) removal of the directing and/or blocking group is strongly influenced by the other substituents and can be insufficiently facile [44OR262, 61QR418, 65MI3, 71S455]. Therefore, the introduction of substituents meta to ortho/para directing groups remains a challenge for organic chemists.

Since directed lithiation is highly regioselective and a variety of substituents can be subsequently introduced, use of directed lithiation would be a prospective solution to the problem. The aim of the present investigation was to identify a new ortho-directing group which, after enabling regiospecific metallation at its ortho position, could be removed easily under mild conditions. It was envisaged that this concept could form the basis of a useful synthetic method for the regiospecific construction of diversely functionalized meta-substituted aromatics from immediate precursors consisting of aromatics substituted in the para or ortho position with such a directing group. The consequence of the strategy is illustrated in Scheme 4.2, where **4.6** is obtained from either an aromatic, **4.5**, initially substituted in its para-position with such a directing group, or an aromatic, **4.7**, initially substituted in its ortho-position.



4.5 **4.6** **4.7**

X = *ortho*/*para*-directing group

Y = incorporated directing group, subsequently eliminated

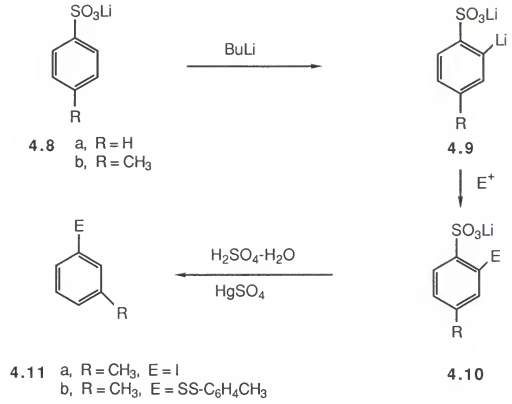
E = the new substituent introduced

Scheme 4.2

If the chosen directing group can itself be introduced easily into the ortho- or para-position of a monosubstituted benzene, in combination with the above sequence, this clearly would allow, for example, the conversion of a monosubstituted benzene into a meta-disubstituted benzene.

A somewhat similar strategy was proposed earlier by Martin and Figuly [80JOC3728] who found that lithium arenesulfonates (**4.8**) could be selectively ortho-lithiated to give the dilithiated species (**4.9**) which, on quenching with a variety of electrophiles, gave access to the corresponding trisubstituted benzenesulfonic acid derivatives (**4.10**). Desulfonation of the sulfonic acid group under acidic conditions ($HgSO_4$-H_2SO_4) gives the meta-substituted benzene derivatives (**4.11**) in good yields (Scheme 4.3).

However, although this method has its own merits including that the lithiation reaction takes place smoothly (10 min at 0 °C) and the dilithiated species are reasonably stable (-20 °C up to three weeks), its drawbacks include low solubility of lithium sulfonates in organic solvents, difficulty in separation of the sulfonic acid intermediates (**4.10**) (yields of **4.10** are based on the ^{1}H-NMR peak ratios), and relative inaccessibility of the starting materials.



4.8 a, R = H
b, R = CH_3

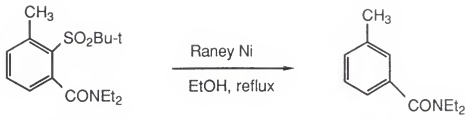
4.9

4.11 a, R = CH_3, E = I
b, R = CH_3, E = SS-$C_6H_4CH_3$

4.10

Scheme 4.3

More recently, Snieckus et al. [89JOC24] reported that the t-butyl sulfone group may act as a latent directed metallation group for the provision of meta-substituted aromatics and showed one example where the sulfone group was hydrolysed (Raney Ni in refluxing ethanol for 15 hr) to furnish a meta-substituted benzene derivative (**4.13**) in a yield of 55% (Scheme 4.4). In comparison with the sulfonic acid group, t-butyl sulfone is more difficult to remove and the starting materials are generally less accessible.



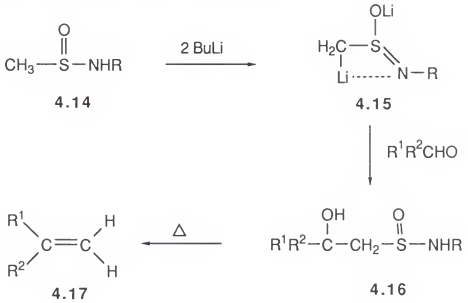
4.12 **4.13**

Scheme 4.4

Sulfinamides have been known for many years [23CB553], but relatively few reactions have been studied in any depth [79MI1, 71MI1]. In general, sulfinamides are much less stable than sulfonamides; they hydrolyze readily in aqueous acid or base to give the corresponding sulfinic acids and amines [35JA2172, 58JOC805]. Nucleophiles react readily with sulfinamides at the sulfur atom, as evidenced by this easy hydrolysis and also by the reaction of N,N-dimethyl-p-toluenesulfinamide with methyllithium to form methyl p-tolyl sulfoxide [68JA6852, 68CC253, 68JA3865]. However, in a mono-N-substituted sulfinamide, nucleophilic attack at sulfur should be discouraged by anion formation, and the strong coordinating and electron-withdrawing properties [71CA150938z, 85MRC424] of sulfinamide groups suggest that treatment with an

appropriate lithiating agent might provide access to stabilized dianions.

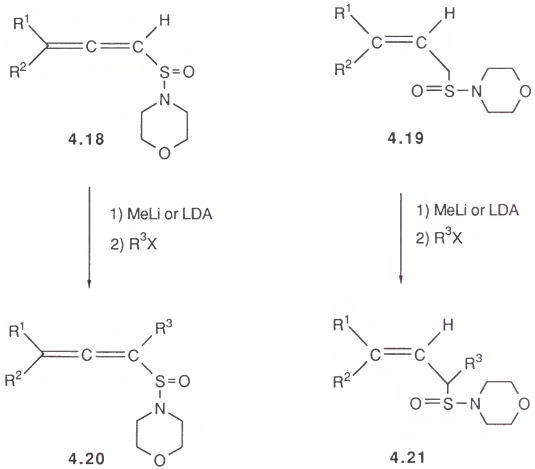
In the earlier studies, Corey and Durst [66JA5656] found that N-methanesulfinamides (**4.14**) can undergo lithiation with two equivalents of butyllithium to give the dilithiated species (**4.15**) which react further with various aldehydes and ketones to give the corresponding adducts (**4.16**). These adducts, on heating at their melting points, readily eliminate the sulfinamide group to afford terminal olefins (**4.17**) (Scheme 4.5).



Scheme 4.5

Even in the case of an N,N-disubstituted sulfinamide, under suitable reaction conditions, the lithiation could still occur at the adjacent carbon instead of the nucleophilic attack at the sulfur atom. More recently, Julia et

al [89TL1963, 89TL4965] reported the lithiation studies of allenic sulfinamides (**4.18**) and β,γ-unsaturated sulfinamides (**4.19**) and found that these sulfinamides can be lithiated smoothly at the adjacent carbons by treatment with methyllithium or LDA. The lithiated derivatives react with a variety of alkyl halides to give the corresponding alkylated products (**4.20**) and (**4.21**) in good yields (Scheme 4.6).



Scheme 4.6

These conclusive results adumbrate that the use of sulfinamides as ortho-directing groups in the aromatic metallation is feasible. Since desulfination is a general and readily occurring reaction, in combination with the lithiation manipulation, it would lead to the success of the strategy outlined in Scheme 4.2.

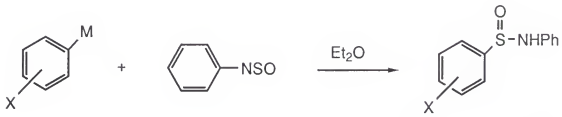
4.2 Results and Discussion

4.2.1 Preparation of N-Phenylarenesulfinamides (4.24)

Sulfinamides have been generally prepared by the treatment of sulfinyl chlorides with amines [35JA2172, 58JOC805, 64USP3253993] or by the treatment of thionylamines with appropriate Grignard or organometallic reagents [26JA2399, 59CB1910, 71JA1178, 74SC137, 76SC129]. Since thionylamines are readily available from the reaction of amines with thionyl chloride [1893LA187, 67AG(E)149, 68MI1] and the Grignard reagents are easily accessible by conventional methods, the latter method appears to be the most convenient.

The preparation of N-phenylarenesulfinamides (**4.24a-d**) was easily accomplished by treatment of commercially available thionylaniline (**4.23**) with the appropriate aryl Grignard or aryllithium (**4.22a-d**) in diethyl ether solution, according to the literature

procedure [59CB1910] (Scheme 4.7). In the case of sulfinamide (**4.24d**), the o-lithioanisole (**4.22d**) was obtained by treatment of anisole with butyllithium in refluxing diethyl ether overnight. All the sulfinamides **4.24a-d** were obtained in high yields (70-90%) and they are stable compounds having fine-crystal forms after recrystallization and can be kept for long periods without decomposition.



4.22 **4.23** **4.24**

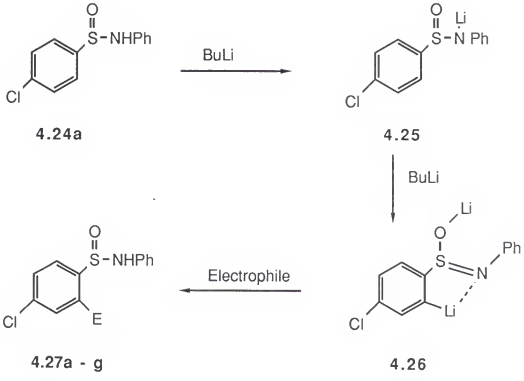
a, X = p-Cl, M = MgCl
b, X = p-CH_3, M = MgBr
c, X = H, M = MgBr
d, X = o-OMe, M = Li

a, X = p-Cl
b, X = p-CH_3
c, X = H
d, X = o-OMe

Scheme 4.7

4.2.2 Lithiation of N-Phenylarenesulfinamides (4.24a-d)

The lithiation investigation was initially carried out by treatment of p-chlorosulfinanilide (4.24a) with 2.1 equiv. of butyllithium in tetrahydrofuran at low temperature followed by quenching with deuterium oxide (D_2O) (Scheme 4.8). The first equivalent of butyllithium was added slowly at -78 °C and a precipitate immediately formed indicating the formation of N-lithiated sulfinamide salt (4.25). After addition of the remaining butyllithium at -78 °C, the precipitate gradually dissolved to give a bright yellow solution. In order to complete the lithiation, the solution was kept at -20 °C for 20 min and then quenched with D_2O.

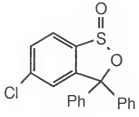


Scheme 4.8

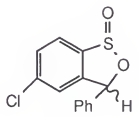
Examination of the crude product (**4.27a**) showed quantitative ortho lithiation, as evidenced by the integral ratios and by the coupling patterns in the 200 MHz ^{1}H-NMR spectrum. Sulfinamide **4.24a** exhibited an ^{1}H-NMR spectrum having a well-resolved AA'BB' pattern in the δ 7.60-7.76 ppm region. The downfield resonance was assigned to the protons ortho to the sulfinamide substituent due to its deshielding effect [85MRC424]. After quenching with D_2O, the product **4.27a** showed clean attenuation of the downfield proton signal and broadening of the upfield signal indicating deuterium incorporation ortho to the sulfinamide group. The integral of the downfield proton resonance is equal to one proton and the integral of upfield proton resonance is equal to two protons.

This success led to an extensive study with other electrophiles and as expected, the dilithiation of sulfinamide **4.24a** was indeed readily accomplished by the addition of 2.1 equiv. of butyllithium in tetrahydrofuran at low temperatures as in the case of deuteration. Addition of appropriate electrophiles to solutions of the dilithiated species **4.26** provided a variety of derivatives substituted ortho to the sulfinamide group in good yields (Scheme 4.8). Generally, the reaction mixture was stirred at -78 °C for 2 hr and then allowed to warm to room temperature overnight.

The ortho-substituted sulfinamides (**4.27b**) and (**4.27c**) produced by reactions with benzophenone and benzaldehyde as electrophiles underwent hydrolysis and cyclization during the aqueous workup to give the novel sultines (**4.28**) and (**4.29**), respectively (Figure 4.1).



4.28



4.29

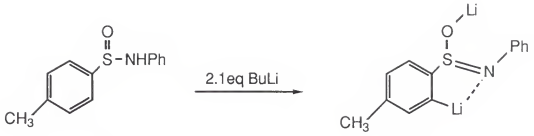
Figure 4.1 Sultines **4.28** and **4.29**

The sulfur atom in sultine **4.28** is stereogenic and hence the two phenyl groups are nonequivalent. As expected, the ^{13}C-NMR spectrum of **4.28** showed fourteen signals downfield in the aromatic region five of which were quaternary carbons as confirmed by an APT experiment. These eventually confirmed the suggested structure.

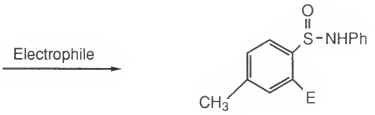
Sultine **4.29** has two chiral centers and therefore a mixture of two diastereomers was expected. Thin layer

chromatography of the crude product showed two spots with very close R_f values (∇R_f = 0.2, $CHCl_3$/hexane, 80:20, v/v) and the separation of the mixture would have been difficult. The ^{1}H-NMR spectrum of the crude product was very complicated and the complete assignments of the signals proved impossible. The ^{13}C-NMR spectrum of the crude product did show the expected signals in which two characteristic signals of the methine carbons appeared at 91.7 and 94.8 ppm, respectively. However, after recrystallization from diethyl ether and hexane, both ^{1}H- and ^{13}C-NMR spectra showed only one diastereomer. Attempted isolation and purification of the other isomer from the filtrate containing a mixture of impurities failed. Because of the lack of comparable literature data on such sultines, the configuration of the isomer obtained has not been determined.

Treatment of **4.24b** with butyllithium at -78 °C and then aging at -10 °C for four hours (compare with **4.24a**) gave a bright reddish-orange solution of the dianion (Scheme 4.9). After quenching with D_2O, the ^{1}H-NMR spectrum of the product showed attenuation of the downfield proton signal and broadening of the upfield proton signal of the AA'BB' system. The downfield resonance was equivalent to 1.28 protons and the upfield resonance to 2.00 protons. This result corresponded to 72% metallation ortho to the sulfinamide substituent.



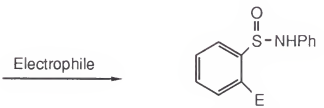
4.24b **4.30**



4.31a - c

Scheme 4.9

4.24c **4.33**



4.34a - d

Scheme 4.10

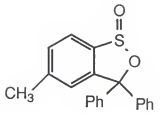


Figure 4.2 Sultine **4.32**

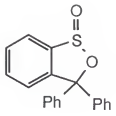


Figure 4.3 Sultine **4.35**

As in the case of **4.24a**, the quenching of dianion **4.30** with benzophenone gave the product **4.31b** which underwent cyclization during the workup to afford the sultine (**4.32**) (Figure 4.2). Again, the ^{13}C-NMR spectrum of **4.32** displayed fourteen resonances in the aromatic region of which five were quaternary carbons as indicated by the APT spectrum. The ^{1}H-NMR spectrum of **4.32** clearly showed the expected ratio (3:15) of the methyl protons to the aromatic protons, unequivocally elucidating the formation of **4.32**.

The lithiation of sulfinamide (**4.24c**) was accomplished by treatment with 2.1 equivalent of butyllithium at -20 °C for 3 hr followed by aging at 0 °C for 1 hr. The addition of various electrophiles to solutions of the dilithiated species (**4.33**) afforded the corresponding ortho-substituted sulfinamides (**4.34**) in good yields (Scheme 4.10). Again, sultine (**4.35**) (Figure 4.3) was isolated as the sole product after the workup and was characterized by NMR spectroscopy.

Table 4.1. Reaction of Dilithiated Sulfinamides (4.24a-d) with Electrophiles

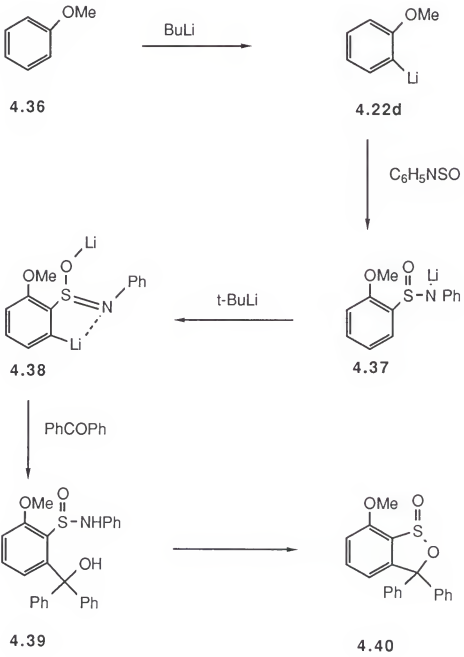
Starting sulfinamide	Lithiation conditions(hr)	Electrophile	Product	Yield(%)	M.p. (°C)
4.24a	-78 to -20 °C (0.5)	D_2O	4.27a	83(100)[a]	158-159
4.24a	-78 to -20 °C (0.5)	$(C_6H_5)_2CO$	4.27b(4.28)	87	160-162
4.24a	-78 to -20 °C (0.5)	C_6H_5CHO	4.27c(4.29)	83	136-138
4.24a	-78 to -20 °C (0.5)	$(C_6H_5S)_2$	4.27d	78	168-169
4.24a	-78 to -20 °C (0.5)	CH_3I	4.27e	89	129-130
4.24a	-78 to -20 °C (0.5)	I_2	4.27f	75	145-147
4.24a	-78 to -20 °C (0.5)	$(CH_3)_3CNCO$	4.27g	68	195-197
4.24b	-78 to -10 °C (4)	D_2O	4.31a	72[a]	136-137
4.24b	-78 to -10 °C (4)	$(C_6H_5S)_2$	4.31c	61	120-122
4.24b	-78 to -10 °C (4)	$(C_6H_5)_2CO$	4.31b(4.32)	60	152-154
4.24c	-20 to 0 °C (4)	$(C_6H_5)_2CO$	4.34a(4.35)	81	125-126
4.24c	-20 to 0 °C (4)	CH_3I	4.34b	76	105-109
4.24c	-20 to 0 °C (4)	$(CH_3)_3CNCO$	4.34c	87	158-160
4.24c	-20 to 0 °C (4)	$(C_6H_5S)_2$	4.34d	72	148-150
4.24d	-40 to -20 °C (1)	$(C_6H_5)_2CO$	4.40	53[b]	138-140

[a]. NMR yield. [b]. Synthesized by one-pot procedure.

In suitable cases, a mono-substituted benzene can be converted in a one-pot sequence into the dilithiated sulfinamide. Thus, compound (**4.40**) was synthesized without isolation of intermediates from anisole (**4.36**), which was directly treated with butyllithium in refluxing ether to give o-lithioanisole (**4.22d**) (Scheme 4.11). After the successive addition of thionylaniline and of t-butyllithium, the dianion species (**4.38**) reacted with benzophenone to give sultine (**4.40**) in an overall yield of 53%. Analogously to the results of the lithiation of o-methoxybenzamide [77JOC1823, 79JOC4463, 82JA5531, 83JOC1565], metallation of the o-methoxysulfinamide occurred ortho to the sulfinamide function and no evidence for by-product formation was found.

The metallation results of sulfinamides (**4.24a-d**) are given in Table 4.1. As summarized in Table 4.1, the effects of the para substituents on the ease of metallation are clearly seen in both the time and the temperature of the metallation and on the yield of product. A chloro substituent accelerates the rate of metallation substantially as shown by comparison with hydrogen and methyl substituents, a result in agreement with observations made with benzamides [82JA5531, 83JOC1565] and thiobenzamides [76JOC4029]. Table 4.1 also shows the yield for each compound along with physical data. A variety of electrophiles were employed to give, in

general, good yields of the products. All new compounds were characterized by their ^{1}H- and ^{13}C-NMR spectra and by elemental analysis (see Experimental section).

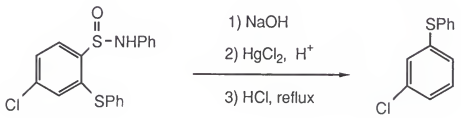


Scheme 4.11

4.2.3 Desulfination of Trisubstituted Sulfinamides

Desulfination was readily accomplished by using either of two known procedures:

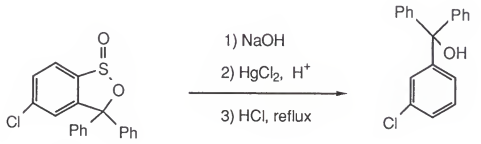
(i) Easy hydrolysis, followed by mercuridesulfination [56JA5357], an effective method for the removal of sulfinic acid groups. Thus, compound **4.27d** was refluxed in a dilute sodium hydroxide solution (0.25 N) to give the sodium sulfinate which (without isolation) was treated with mercuric chloride in an acidic solution, to yield compound (**4.41**) in yield of 81% (Scheme 4.12). The chloro substituent as well as the thiophenyl moiety remained intact under these reaction conditions.



4.27d **4.41**

Scheme 4.12

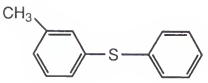
Desulfination of sultines can also be accomplished by mercuridesulfination. Thus sultine **4.28** was hydrolysed and desulfinated with mercuric chloride in a refluxing hydrochloric acid-ethanol solution, leading to the corresponding alcohol (**4.42**) in 72% yield (Scheme 4.13).



4.28 **4.42**

Scheme 4.13

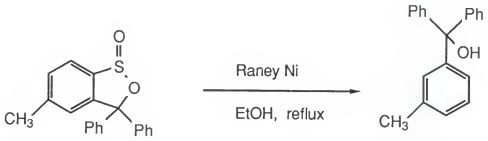
Similarly, the meta-disubstituted benzene (**4.43**) (Figure 4.4) was obtained in good yield (85%) by the same method from sulfinamide **4.31c**.



4.43

Figure 4.4 m-Tolyl phenyl sulfide

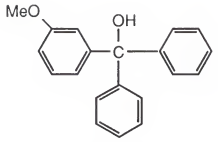
(ii) Desulfination of sulfinamides was also carried out by reductive desulfination using Raney-Ni in refluxing ethanol [72T5017]. A representative example was the desulfination of compound **4.32** which was dissolved in an ethanolic sodium hydroxide solution (pH = 10) and refluxed with Raney-Ni overnight to give carbinol (**4.44**) in 87% yield (Scheme 4.14).



4.32 **4.44**

Scheme 4.14

Carbinol (**4.45**) (Figure 4.5) was also obtained in good yield (78%) by this method from sultine **4.40**. However, contrary to method (i) the chloro substituent in compound **4.28** does not survive under the Ra/Ni conditions for desulfination.



4.45

Figure 4.5 m-Methoxyphenyldiphenylcarbinol

Table 4.2 Desulfination of ortho-Substituted Benzenesulfinamides (sultines)

Sulfinamide	Method[a]	Product	Yield (%)[b]
4.27d	A	4.41	81
4.28	A	4.42	72
4.31c	A	4.43	85
4.32	B	4.44	87
4.40	B	4.45	78

a. A: Desulfination using mercuric chloride in acidic solution; B: Reductive desulfination using Raney-Ni.

b. Isolated yield.

The results of desulfinations using both methods are listed in Table 4.2. As shown in Table 4.2, both methods gave desulfinated products in good yields. All the products were characterized by their ^{1}H-, ^{13}C-NMR spectra and mass spectra, as well as by comparison with literature data.

4.3 Conclusions

The directed lithiation of sulfinamides has been successfully achieved. Lithiation, followed by eletrophilic substitution, clearly introduces a variety of substituents ortho to the sulfinamide group. The subsequent desulfination is a readily occurring reaction and gives high yields of meta-disubstituted benzene derivatives. The whole leads to the success of the strategy according to which a meta-disubstituted benzene can be synthesized from a mono-substituted benzene containing an ortho/para directing group.

In view of the easy attachment and removal of sulfinamide groups, the expanding scope of ortho-directed metallation, and the increasing number of directing groups, our method should have broad synthetic utility for aromatic and heterocyclic transformations involving the introduction of meta-substituents. The high yields, easy

manipulation and considerably mild conditions further demonstrate the accessibility and the utility of the method.

4.4 Experimental

4.4.1 General

The apparatus and general procedures applied in this Chapter are identical to those described in Chapter II.

Diethyl ether was predried with molecular sieves 4 Å and freshly distilled from sodium/benzophenone ketyl before use. Thionylaniline was purchased from Aldrich and used without further purification.

4.4.2 Preparation of Sulfinamides (4.24a-d)

General Procedure. To a solution of the Grignard reagent (0.05 mol) in dry diethyl ether (100 mL), N-thionyaniline (7.10 g, 0.05 mol) in diethyl ether (10 mL) was added dropwise via a syringe at 0 °C. The reaction mixture was stirred at this temperature for 2 hr and allowed to warm to room temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride (30 mL) and extracted with tetrahydrofuran (3 x 30 mL). The combined extracts were dried with sodium sulfate and evaporated under reduced pressure to give the

crude product which was further purified as described for each particular compound. Sulfinamides (**4.24a-c**) were prepared by this way whereas sulfinamide (**4.24d**) was prepared by an alternative way as described below.

4-Chloro-N-phenylbenzenesulfinamide (**4.24a**). Plates (92%) (recrystallized from chloroform and petroleum ether, 90:10, v/v), m.p. 158-159 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.41 (s, 1 H, NH), 7.71 (d, J = 10 Hz, 2 H), 7.66 (d, J = 10 Hz, 2 H), 6.91-7.29 (m, 5 H); ^{13}C-NMR (DMSO-d_6) δ 143.5, 141.5, 135.9, 129.2, 129.0, 127.6, 122.3, 118.0.

Anal. Calcd for $C_{12}H_{10}ClNOS$: C, 57.26; H, 4.00; N, 5.56. Found: C, 57.21; H, 4.05; N, 5.42.

4-Methyl-N-phenylbenzenesulfinamide (**4.24b**). Plates (71%) (recrystallized from benzene and hexane, 90:10, v/v), m.p. 135-136 °C; lit. [59CB1910] m.p. 137-138 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.23 (s, 1 H, NH), 7.61 (d, J = 10 Hz, 2 H), 7.38 (d, J = 10 Hz, 2 H), 6.83-7.22 (m, 5 H), 2.37 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 141.8, 141.6, 140.8, 129.5, 129.1, 125.5, 121.9, 117.7, 20.8 (CH_3).

N-Phenylbenzenesulfinamide (**4.24c**). Needles (82%) (recrystallized from chloroform and hexane, 85:15,v/v), m.p. 113-114 °C; lit. [59CB1910] m.p. 113-114 °C; ^{1}H-NMR

($CDCl_3$, TMS) δ 7.05-7.75 (m, 10 H), 6.59 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 144.5, 140.7, 131.3, 129.4, 129.0, 125.6, 123.5, 118.9.

2-Methoxy-N-phenylbenzenesulfinamide (**4.24d**). Anisole (5.41 g, 0.05 mol) was dissolved in diethyl ether (50 mL) and butyllithium (20 mL, 0.05 mol, 2.5 M in hexane) was added slowly via a syringe at room temperature under argon. The mixture was refluxed overnight and then cooled to -20 °C. Thionylaniline (7.10 g, 0.05 mol) in dried diethyl ether (15 mL) was added slowly and the mixture was stirred at -20 °C for 4 hr and warmed to room temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride (20 mL) and extracted with ether (4 x 30 mL). The combined extracts were dried with sodium sulfate and evaporated under reduced pressure to give a solid which was recrystallized from chloroform and petroleum ether (90:10, v/v) to give 8.66 g (70%) of the pure product as plates, m.p. 122-124 °C; ^1H-NMR ($CDCl_3$, TMS) δ 6.64-7.99 (m, 10 H, aromatic protons and NH), 3.84 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 155.9, 141.2, 132.7, 128.9, 125.6, 122.6, 120.6, 118.4, 114.8, 111.1, 55.6 (CH_3).

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 62.98; H, 5.36; N, 5.68.

4.4.3 General Procedure for the Preparation of Substituted Benzenesulfinamides (**4.27a-g**)

p-Chloro-N-phenylbenzenesulfinamide (**4.24a**) (5 mmol) was dissolved in tetrahydrofuran (45 mL) in a two necked Schlenk reactor under an argon atmosphere and cooled to -78 °C. Butyllithium (4.2 ml, 10.5 mmol, 2.5 M in hexane) was added dropwise. The reaction mixture was stirred at -78 °C for 20 min and then allowed to warm to -20 °C, and stirred at -20 °C for 20 min. The reaction mixture was recooled to -78 °C and the electrophile (10 mmol) in tetrahydrofuran (5 mL) was added slowly. The reaction mixture was kept at -78 °C for 3-4 hr and allowed to warm to room temperature overnight. Aqueous hydrochloric acid (10%; 10 mL) or water was added to quench the reaction and the solution was extracted with ether (3 x 15mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. After the solvent had been removed under reduced pressure, the crude product was further purified as described for each particular compound.

4-Chloro-2-deuteriobenzenesulfinanilide (**4.27a**). Plate (83%) (recrystallized from $CHCl_3$ and petroleum ether, 85:15, v/v), m.p. 158-159 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.39 (s, 1 H, NH, ex), 7.58-7.82 (m, 3 H), 6.92-7.35 (m, 5 H); ^{13}C-NMR (DMSO-d_6) δ 143.4, 141.5, 135.8, 129.1, 129.0,

128.9, 127.5, 122.3, 117.9. MS (HR) for $C_{12}H_9DClNOS$ calcd. 252.0234; found: 252.0226.

5-Chloro-3,3-diphenyl-3H-2,1-benzoxathiole 1-oxide (**4.28**). Needles (87%) (recrystallized from $CHCl_3$ and hexane, 90:10, v/v), m.p. 160-162 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.18-7.79 (m, 13 H); ^{13}C-NMR ($CDCl_3$) δ 145.4, 145.1, 141.9, 141.5, 138.8, 130.3, 129.0, 128.6, 128.5, 127.6, 127.5, 125.7, 125.3, 104.4 (COSO). MS (HR) for $C_{19}H_{13}ClO_2S$ calcd. 340.0325; found: 340.0326.

Anal. Calcd for $C_{19}H_{13}ClO_2S$: C, 66.96; H, 3.84. Found: C, 66.75; H, 3.91.

5-Chloro-3-phenyl-3H-2,1-benzoxathiole 1-oxide (**4.29**). Needles (83%) (recrystallized from $CHCl_3$ and hexane, 80:20, v/v), m.p. 136-138 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.08-7.61 (m, 8 H), 6.56 (s, 1 H, CH); ^{13}C-NMR ($CDCl_3$) δ 146.1, 143.5, 138.9, 135.8, 129.9, 129.2, 129.1, 127.9, 124.5, 124.0, 91.8 (CHOSO). MS (HR) for $C_{13}H_9ClO_2S$ calcd. 264.0012; found: 264.0024.

Anal. Calcd for $C_{13}H_9ClO_2S$: C, 58.98; H, 3.43. Found: C, 58.92; H, 3.34.

4-Chloro-2-phenylthiobenzenesulfinanilide (**4.27d**). Needles (78%) (recrystallized from $CHCl_3$ and hexane, 85:15, v/v), m.p. 168-169 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.20 (s, 1 H, NH,

ex), 6.75-7.90 (m, 13 H); ^{13}C-NMR (DMSO-d_6) δ 142.1, 141.7, 137.6, 136.4, 132.9, 131.9, 130.0, 129.3, 129.2, 129.0, 127.4, 127.0, 122.2, 117.3.

Anal. Calcd for $C_{18}H_{14}ClNOS_2$: C, 60.07; H, 3.92; N, 3.89. Found: C, 59.65; H, 3.92; N, 3.81.

4-Chloro-2-methylbenzenesulfinanilide (**4.27e**). Needles (89%) (recrystallized from $CHCl_3$ and petroleum ether, 90:10, v/v), m.p. 129-130 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.98-7.85 (m, 8 H), 6.81 (s, 1 H, NH, ex), 2.38 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 140.7, 140.5, 137.6, 137.2, 130.7, 129.3, 126.5, 125.6, 123.3, 118.3, 18.2 ($\underline{C}H_3$).

Anal. Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H, 4.55; N, 5.27. Found: C, 58.67; H, 4.48; N, 5.25.

4-Chloro-2-iodobenzenesulfinanilide (**4.27f**). Needles (75%) (recrystallized from benzene and petroleum ether, 85:15, v/v), m.p. 145-147 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 8.23 (bs, 1 H, NH), 6.92-8.01 (m, 8 H); ^{13}C-NMR (DMSO-d_6) δ 145.3, 142.0, 138.4, 136.5, 128.6, 128.0, 122.2, 117.1, 95.7. MS (HR) for $C_{12}H_9ClINOS$ calcd. 376.9138; found: 376.9156.

4-Chloro-2-t-butylcarbamoylbenzenesulfinanilide (**4.27g**). Needles (68%) (recrystallized from ethyl acetate), m.p. 195-197 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.16 (s, 1 H, NH), 7.39-8.32 (m, 8 H), 1.39 (s, 9 H, CH_3); ^{13}C-NMR (DMSO-d_6)

δ 164.4 (CONH), 142.5, 142.3, 137.8, 135.4, 129.6, 129.0, 128.2, 127.0, 121.9, 117.3, 51.2 [$\underline{C}(CH_3)_3$], 28.3 ($\underline{C}H_3$).

Anal. Calcd for $C_{17}H_{19}ClN_2O_2S$: C, 58.20; H, 5.46; N, 7.98. Found: C, 58.38; H, 5.37; N, 7.65.

4.4.4 General Procedure for the Preparation of Substituted Benzenesulfinamides (**4.31a-c**)

Similar to the preparation of sulfinamides **(4.27a-g)**, except the lithiation temperature and time are different (see Table 4.1). The crude product was further purified as described for each particular compound.

4-Methyl-2-deuteriobenzenesulfinanilide (**4.31a**). Needles (72%) (recrystallized from $CHCl_3$ and hexane, 85:15, v/v), m.p. 136-137 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.42 (d, J = 10 Hz, 1 H), 6.95-7.39 (m, 7 H), 6.63 (s, 1 H, NH, ex), 2.41 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 141.7, 141.5, 140.8, 129.7, 129.6, 129.4, 125.5, 123.4, 118.8, 21.4 ($\underline{C}H_3$). MS (HR) for $C_{13}H_{12}DNOS$ calcd: 232.0780; found: 232.0775.

5-Methyl-3,3-diphenyl-3H-2,1-benzoxathiole 1-oxide (**4.32**). Needles (60%) (recrystallized from ether and hexane, 90:10, v/v), m.p. 152-154 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.19-7.73 (m, 13 H), 2.42 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 144.0, 143.6, 143.1, 142.6, 142.3, 130.8, 128.6, 128.4, 128.3, 128.2, 127.7, 127.6, 125.8, 123.8, 104.2 ($\underline{C}OSO$),

21.8 ($\underline{C}H_3$).

Anal. Calcd for $C_{20}H_{16}O_2S$: C, 74.97; H, 5.03. Found: C, 74.95; H, 5.00.

4-Methyl-2-phenylthiobenzenesulfinanilide (**4.31c**). Needles (61%) (column chromatography from $CHCl_3$ and hexane, 80:20, v/v), m.p. 120-122 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.87-7.98 (m, 13 H), 2.38 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 141.6, 141.4, 141.0, 140.9, 133.2, 131.5, 129.6, 129.3, 129.2, 128.5, 127.6, 125.6, 123.2, 118.7, 21.3 ($\underline{C}H_3$).

Anal. Calcd for $C_{19}H_{17}NOS_2$: C, 67.23; H, 5.05; N, 4.13. Found: C, 67.19; H, 5.44; N, 4.31.

4.4.5 General Procedure for the Preparation of Substituted Benzenesulfinamides (**4.34a-d**)

Similar to the preparation of sulfinamides (**4.27a-g**), except the lithiation temperatures and times are different (see Table 4.1). The crude product was further purified as described for each particular compound.

3,3-Diphenyl-3H-2,1-benzoxathiole 1-oxide (**4.35**). Needles (81%) (recrystallized from $CHCl_3$ and hexane, 85:15, v/v), m.p. 125-126 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.18-7.69 (m, 14 H); ^{13}C-NMR ($CDCl_3$) δ 146.5, 143.1, 142.5, 142.1, 132.2, 129.7, 128.7, 128.4, 128.3, 127.6, 127.5, 125.5,

124.1, 104.6 (COSO).

Anal. Calcd for $C_{19}H_{14}O_2S$: C, 74.48; H, 4.60. Found: C, 74.69; H, 4.61.

2-Methylbenzenesulfinanilide (**4.34b**). Needles (76%) (recrystallized from $CHCl_3$ and hexane, 80:20, v/v), m.p. 105-109 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.94-8.07 (m, 9 H), 6.58 (s, 1 H, NH), 2.23 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 142.0, 141.0, 135.7, 131.1, 130.8, 129.2, 126.4, 123.8, 123.0, 118.1, 18.4 (CH_3).

Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.59; H, 5.32; N, 5.66.

2-t-Butylcarbamoylbenzenesulfinanilide (**4.34c**). Needles (87%) (recrystallized from $CHCl_3$ and hexane, 85:15, v/v), m.p. 158-160 °C; ^{1}H-NMR (DMSO-d_6, TMS) δ 9.08 (s, 1 H, NH), 7.05-8.36 (m, 10 H), 1.46 (s, 9 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 166.0 (CONH), 143.1, 142.8, 136.3, 130.6, 129.8, 129.0, 128.4, 124.7, 121.7, 117.2, 51.0 [$C(CH_3)_3$], 28.4 (CH_3).

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.53: H, 6.37; N, 8.85. Found: C, 64.71; H, 6.31; N, 8.61.

2-Phenylthiobenzenesulfinanilide (4.34d). Needles (72%) (recrystallized from $CHCl_3$ and hexane, 80:20, v/v), m.p. 148-150 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.91-8.12 (m, 14 H),

4.78 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 143.6, 140.9, 135.0, 133.6, 131.6, 131.5, 131.2, 129.0, 128.8, 127.5, 126.8, 125.0, 122.5, 117.9.

Anal. Calcd for $C_{18}H_{15}NOS_2$: C, 66.43; H, 4.65; N, 4.30. Found: C, 66.76; H, 4.55; N, 4.19.

4.4.6 One-pot procedure for the Preparation of 7-Methoxy-3,3-diphenyl-3H-benzoxathiole 1-oxide (4.40)

Anisole (1.08 g, 10 mmol) was dissolved in dry ethyl ether (20 mL, dried over sodium/benzophenone, freshly distilled) in a two necked Schlenk reactor and butyl-lithium (4.0 mL, 10 mmol, 2.5 M in hexane) was added dropwise at 25 °C. The mixture was refluxed for 14 hr. The reaction mixture was cooled to -78 °C and thionylaniline (1.39 g, 10 mmol) was added slowly to give a yellow suspension. The mixture was stirred at 25 °C for 30 min and cooled to -40 °C, t-butyllithium (5.9 mL, 10 mmol, 1.7 M in pentane) was added dropwise. The solution turned red-orange and the precipitate gradually dissolved. The mixture was stirred at -40 °C for 10 min, then allowed to warm to -20 °C and stirred at this temperature for 1 hr. The reaction mixture was recooled to -78 °C and benzophenone (1.84 g, 10 mmol) in ethyl ether (5 mL) was added slowly. The reaction mixture was stirred at -78 °C for 3-4 hr and then warmed to room temperature overnight. The reaction was quenched with aqueous HCl (10%; 10 mL),

extracted with ether (3 x 30 mL), washed with brine, and dried over Na_2SO_4. After evaporation of the solvent an oily residue was obtained. The residue was triturated with ether and hexane to give a white solid which was recrystallized from ether-hexane (90:10, v/v) to give 1.78 g (53%) of compound (**4.40**): m.p. 138-140 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.87-7.50 (m, 13 H), 3.92 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 155.8, 144.9, 141.7, 141.5, 133.8, 127.8, 127.6, 127.5, 126.9, 116.4, 110.4, 104.1 (COSO), 55.3 (CH_3O).

Anal. Calcd for $C_{20}H_{16}O_3S$: C, 71.41; H, 4.80. Found: C, 71.63; H, 4.55.

4.4.7 Desulfination of Substituted Benzenesulfinamides (Sultines)

Mercuridesulfination (method A), General Procedure. The sulfinamide (250 mg) was dissolved in a mixture of NaOH (10 mL, 0.25 N) and ethanol (10 mL, 95%). The mixture was refluxed for 2-3 hr and acidified with acetic acid. Mercuric chloride (0.4 g) was added and the mixture was refluxed for 1 hr to give a precipitate. The precipitate was collected and suspended in a mixture of conc. hydrochloric acid (10 mL) and ethanol (10 mL, 95%). The whole was refluxed for 2-3 hr until the suspension dissolved. The mixture was diluted with water, extracted with benzene (3 x 25 mL), and dried over Na_2SO_4.

Evaporation of the solvent under reduced pressure gave the crude product which was further purified as described for each particular compound.

m-Chlorophenyl phenyl sulfide (**4.41**). A colorless oil was obtained after column chromatography (Et_2O-hexane, 80:20, v/v), lit. [52JCS1168] b.p. 186 °C/30 mmHg; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.08-7.48 (m, 9 H); ^{13}C-NMR ($CDCl_3$) δ 138.8, 134.8, 133.8, 132.2, 129.9, 128.3, 127.9, 127.8, 126.6; MS (m/z, relative intensity) 220 (M^+, 100%); MS (HR) for $C_{12}H_9ClS$ calcd. 220.0113; found: 220.0016.

m-Chlorophenyldiphenylcarbinol (**4.42**). A pale yellow sticky oil (79%) was obtained after workup and the compound was clean as shown by its NMR spectra; lit. [42JOC392] m.p. 53-54 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.85-7.36 (m, 14 H), 3.28 (bs, 1 H, OH, ex); ^{13}C-NMR ($CDCl_3$) δ 145.9, 143.0, 129.5, 129.3, 128.4, 128.0, 127.8, 127.6, 127.5, 126.5, 81.6 (COH). MS (HR) for $C_{19}H_{15}ClNO$ cacld. 294.0812; found: 294.0815.

m-Tolyl phenyl sulfide (**4.43**). A pale yellow oil (85%) was obtained after column chromatography (Et_2O-hexane, 90:10, v/v), b.p. 309-310 °C/760 mmHg; lit. [1895CB2323] b.p. 309.5 °C/760 mmHg; ^{1}H-NMR ($CDCl_3$, TMS) δ 7.15-7.58 (m, 9 H), 2.24 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 138.9, 136.1,

135.2, 131.8, 130.7, 129.1, 128.9, 128.3, 127.9, 126.8, 21.2 ($\underline{C}H_3$).

Hydrodesulfination (method B). General Procedure. The sulfinamide (sultine) (250 mg) was dissolved in a mixture of NaOH (20 ml,0.25 N) and ethanol (20 ml, 95%) and refluxed for 3-4 h with Raney Ni (5 g). The alkaline solution was filtered, acidified with HCl (5%), and extracted with chloroform (3 x 15 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give the crude product which was purified as described for each particular compound.

m-Tolyldiphenylcarbinol (**4.44**). A crystalline solid (87%) was obtained by recrystallization from benzene-petroleum ether (90:10, v/v), m.p. 65-67 °C; lit. [59CJC1402] m.p. 62-65 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.82-7.24 (m, 14 H), 2.78 (bs, 1 H, OH, ex), 2.18 (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 146.9, 137.5, 135.7, 128.4, 127.9, 127.8, 127.7, 127.1, 125.5, 125.2, 81.9 ($\underline{C}OH$), 21.5 ($\underline{C}H_3$).

m-Methoxyphenyldiphenylcarbinol (**4.45**). A crystalline solid (78%) was obtained after recrystallization from ethyl ether, m.p. 88-89 °C, lit. [59CJC1402] m.p. 87-89 °C; ^{1}H-NMR ($CDCl_3$, TMS) δ 6.84-7.52 (m, 14 H), 3.74 (s, 3 H, CH_3), 2.98 (bs, 1 H, OH, ex); ^{13}C-NMR ($CDCl_3$) δ

159.1, 148.4, 146.7, 128.7, 128.6, 127.9, 127.8, 127.6, 127.1, 120.5, 81.8 (COH), 54.9 (CH_3O).

CHAPTER V

SUMMARY

A major part of the work described here was focused on the elaboration of new strategies of direction, protection, and activation in lithiation chemistry. The strategies envisaged were advantageously utilized in the development of new synthetic methods for the preparation of α-substituted heterocyclic azoles (pyrazoles and 1,2,4-triazoles) and for the construction of meta-substituted benzene derivatives. The utilization of benzotriazole as an auxiliary in the synthetic transformations to secondary and tertiary amines, and to N,N-disubstituted hydroxylamines was also investigated.

In Chapter I, the good leaving ability of benzotriazole enabled the development of new and facile methods for the preparation of secondary and tertiary amines, and of N,N-disubstituted hydroxylamines. The nucleophilic displacement of the benzotriazole moieties with Grignard reagents and organolithium reagents in N,N-bis(benzotriazol-1-ylmethyl)amine, -N-alkylamines and -hydroxylamine led to the formation of various secondary and tertiary amines and N,N-disubstituted hydroxylamines

involving two new C-C bonds. The new methods were shown to be of general utility, simplicity and easy accessibility.

In Chapters II and III, the application of hemiaminals and aminals as protecting-activating groups in the α-lithiation of heterocyclic azoles was investigated. The use of formaldehyde as the equivalent of a hemiaminal protecting-activating group was found to be effective in the α-lithiation of pyrazole. The protecting group was readily introduced by the reaction of pyrazole with aqueous formaldehyde or paraformaldehyde under mild conditions. The use of paraformaldehyde is superior to that of aqueous formaldehyde, since the following lithiation can be directly carried out without the pre-purification of the intermediate. The α-lithiation of 1-hydroxymethylpyrazole was smoothly accomplished at low temperature and the α-lithiated species was sufficiently reactive towards a variety of electrophiles. The removal of the hemiaminal was readily achieved by acid-catalyzed hydrolysis or by silica gel assisted fission. Various α-substituted pyrazoles were obtained in moderate to good yields by this new, attractive method. Particularly attractive was the easy introduction and removal of the protecting group, as well as the one-pot manipulation of the whole process.

The directing and activating effects of aminal groups in the α-lithiation of azoles were found to be valuable by

previous results. In the present investigation, the effect of the aminal group to enable α-lithiation of 1-(1-pyrrolidinomethyl)-1,2,4-triazole was shown to be useful. The α-lithiation was readily accomplished at low temperature and a variety of electrophiles was incorporated into the α-position of the triazole. However, in solution the resultant α-substituted 1-(1-pyrrolidinomethyl)-1,2,4-triazoles were shown to exist as equilibrium mixtures of 3-substituted and 5-substituted isomers. In most cases, the 3-substituted isomer is predominant in the equilibrium mixture and probably is exclusive in the solid state, as verified by an X-ray structure analysis of the compound carrying a t-butylcarbamoyl substituent. Further confirmation of such isomerization processes was gathered from cross-over and variable temperature NMR experiments. Lithiation, followed by addition of a dialkyl disulfide afforded the deprotected product as the result of a nucleophilic cleavage of the aminal group by the organosulfide anion formed during the reaction. The removal of the aminal group by acid-catalyzed hydrolysis failed in most cases. Successful results were obtained when reductive elimination using sodium borohydride was applied, thereby accomplishing the ultimate aim of the research.

The introduction of a substituent at the

meta-position to an ortho/para directing group is a classical problem of organic chemistry. A novel synthetic strategy for the construction of diversely functionalized meta-substituted benzene derivatives via directed lithiation was investigated. The directing effect of the sulfinamide group to enable regiospecific metallation at its ortho position was found to be successful. Lithiation, followed by electrophilic substitution, clearly introduced a variety of substituents ortho to the sulfinamide group. An electron withdrawing group (a chloro substituent) can accelerate the rate of metallation substantially as shown by comparison with an electron donating group (a methyl substituent). When a ketone or an aldehyde was used as the electrophile, the cyclized product, a sultine, was obtained. Desulfination was readily achieved by mercuridesulfination or reductive desulfination using Raney-Nickel. However, a halogen substituent did not survive under the Raney-Nickel conditions. This two-step sequence led to the success of the strategy according to which a meta-substituted benzene can be synthesized from a mono-substituted benzene carrying an ortho/para directing group.

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Letter Codes for Journal Titles

Code	Journal Abbreviation
ACR	Acc. Chem. Res.
ACS(B)	Acta Chim. Scand., Ser. B.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AJC	Austr. J. Chem.
BCJ	Bull. Chem. Soc. Jpn.
BSF	Bull. Soc. Chim. Fr.
CA	Chem. Abstr.

CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CJC	Can. J. Chem.
CL	Chem. Lett.
CRV	Chem. Rev.
H	Heterocycles
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta.
JA	J. Am. Chem. Soc.
JCS	J. Chem. Soc.
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JHC	J. Heterocycl. Chem.
JMR	J. Mag. Reson.
JPS	J. Polym. Sci.
LA	Liebigs Ann.
MI	Miscellaneous
MRC	Magn. Reson. Chem.
OM	Organometallics
OR	Org. React.
QR	Quarterly Reviews
RT	Rec. Trav. Chim. Pays-Bas.
SC	Synth. Comm.
S	Synthesis
T	Tetrahedron
TL	Tetrahedron Lett.
USP	U. S. Patent

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BIOGRAPHICAL SKETCH

Ping Lue was born on March 15, 1953, in Hangzhou, China. He was fortunate to complete his primary education before the "Cultural Revolution" which started in 1966 in China. From December 1969 to January 1976, he served as a farmer working on a state farm where he learned how to plant rice, cotton and wheat.

After the "Cultural Revolution", he was able to pursue his college education and received his Bachelor of Science degree in chemistry from the Hangzhou University in April 1982. Then he received his Master of Science degree from the same university in December 1985, under the supervision of Prof. Xun-Jun Zhou.

In January 1987, he enrolled in the Graduate School at the University of Florida and joined the research group of Prof. Alan R. Katritzky in the same year.

He has one elder brother and two elder sisters. He is married to Xiao Ming Xia and has one daughter Jennifer who was born on January 12, 1989, in Gainesville.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chairman
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1990

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